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***Brief course in***

**ORGANIC CHEMISTRY**



*Brief course in*

# ORGANIC

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*Professor of Chemistry, Mississippi State University*

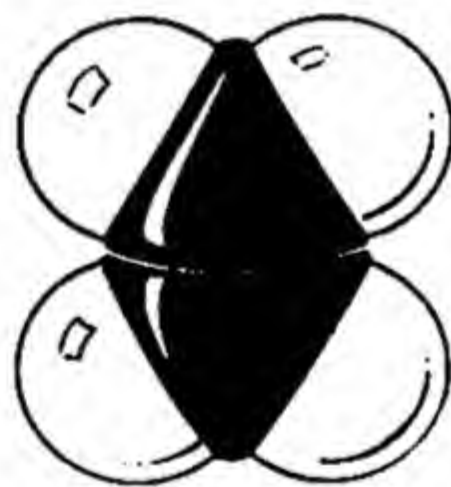
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# CHEMISTRY

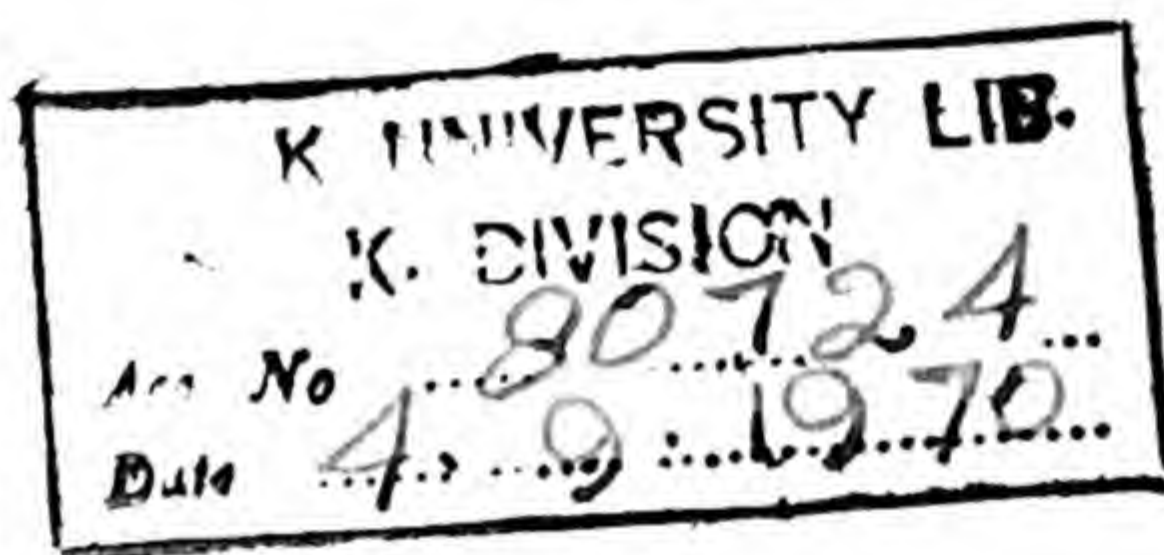


*2<sup>nd</sup> edition*

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## ***Preface***

The order of presentation of the previous edition of this book has been retained. Further experience with the short introductory chapters, designed to orient the student in the language of organic chemistry and to introduce him to fundamental concepts, has been encouraging. To increase their value these chapters have been expanded by the inclusion of additional material; emphasis is placed on the functional groups.

The importance of having the text and laboratory manual combined in a single volume has declined with the improving economic status of students and with the appearance of a number of laboratory manuals that are admirably suited for use in a short course. As a consequence, the laboratory procedures in the first edition have been omitted.

A new feature of the book is the inclusion of questions at the ends of the chapters. They are not intended as memory tests but rather are designed to give the student practice in the *application* of the text material. There are additional illustrations, which include many of molecular models.

Nearly the whole text has been rewritten. Additional examples of reactions are provided, and explanations are presented in more detail. The structural formulas of many compounds of practical importance are given, for it is believed that they will be of especial interest to students who will have occasion to use the substances in the professions for which they are preparing. A few chapters have been eliminated from the earlier edition. Those dealing with ketones and

aldehydes have been combined; the information originally contained in the chapters entitled Industrial Developments in Aromatic Chemistry, Aromatic Compounds, and Natural Products has been incorporated into other chapters. In a few instances the titles of chapters have been altered in accordance with the revision of their contents. New chapters entitled Homologous Series, Naturally Occurring Esters, and Sulfur Compounds are included. Some of the material for these chapters appeared in other parts of the earlier edition, but supplemental information has been added.

We wish to thank the instructors who have made suggestions for the improvement of the earlier edition. Gratitude is also expressed to the following for their help: Billups Allen, Eldon A. Behr, S. J. Brewer, and E. E. Howe.

LYELL C. BEHR  
REYNOLD C. FUSON  
HAROLD R. SNYDER

*March 1959*

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# **Introduction**     *Organic chemistry*

A large proportion of animal and plant tissues is made up of compounds which contain carbon combined with two or more of the following elements: hydrogen, oxygen, nitrogen, halogen, phosphorus, sulfur, and, less frequently, others. Compounds of this group came to be known as organic because they originated in plant and animal organisms. As the study of organic compounds progressed, it became apparent that most of them are nonionic substances and, consequently, have chemical and physical properties widely different from those of the ionic salts and the acids and bases which are typical of inorganic compounds. Another basis of distinction between the two fields is that the inorganic compounds do not contain both *carbon* and *hydrogen*. Organic compounds which contain only carbon and hydrogen are known as *hydrocarbons*. Organic chemistry may be defined as *the science which deals with the hydrocarbons and their derivatives*.

**► SOURCES OF ORGANIC COMPOUNDS**

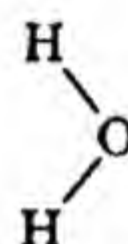
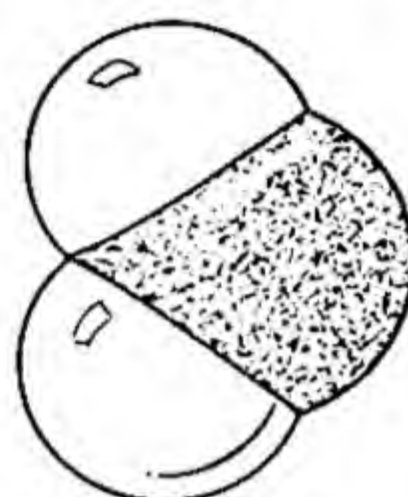
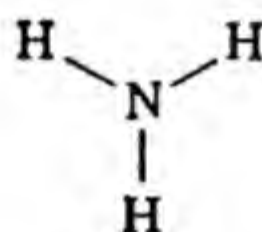
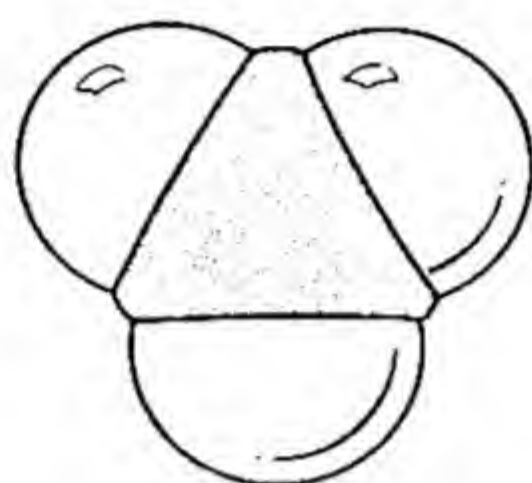
Early workers in the field of organic chemistry devoted themselves almost entirely to the isolation of substances from plants and animals. Thus from plants came rubber, vegetable oils, carbohydrates, alkaloids, perfumes, camphor, and alcoholic beverages. Animals produced musk and civet perfumes, fats, glue, urea, and oils. In more recent times man has turned his attention also to petroleum and coal. From petroleum come gasoline, lubricating oils, paraffin wax, and diesel and jet fuels. Coal yields coke and coal tar, a substance which has proved to be the source of a vast array of useful products.

**► CLASSIFICATION**

The study of organic chemistry has been facilitated greatly by the development of a system of classification for the large number of compounds which has been discovered. It has been found that organic compounds can be divided into groups, such as hydrocarbons, alcohols, aldehydes, acids, bases, and esters, on the basis of similarities in structure and chemical properties. The chemical properties of the compounds within a single class are similar so that once the properties of a representative member of a series are known the properties of the others in that series can usually be predicted.



## *chapter 1* Valence and structure



Though the typical valence of inorganic compounds is ionic, many of those commonly met with are covalent. In the molecules depicted above the central atom is joined to hydrogen by a single bond which represents a pair of shared electrons. It is of interest that both the ammonia and water molecules are planar. The angle between the valence bonds of the oxygen atom in water is  $105^\circ$ .

Although no one can state exactly the number of known organic compounds, it is probably something near 2,000,000, a figure about twenty times the known number of inorganic compounds. This ratio is remarkable, for organic chemistry deals with the compounds of one element—carbon—whereas inorganic chemistry treats the compounds of the other 100 or so elements. For a better understanding of this paradox it is desirable that we examine the differences in properties of these two classes and gain some insight into the ways in which the atoms in compounds are held together.

A comparison of the properties of a typical organic compound and a typical inorganic substance reveals these general differences:

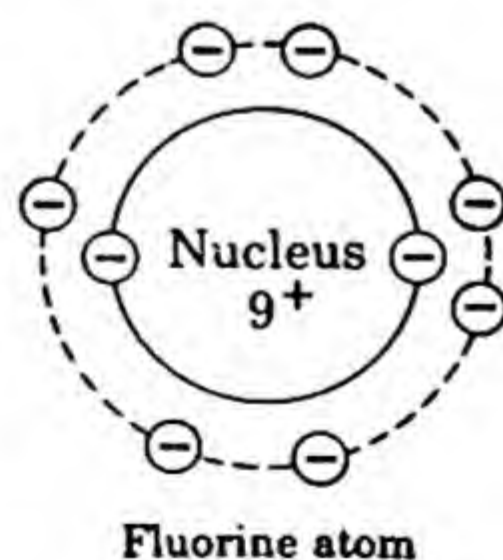
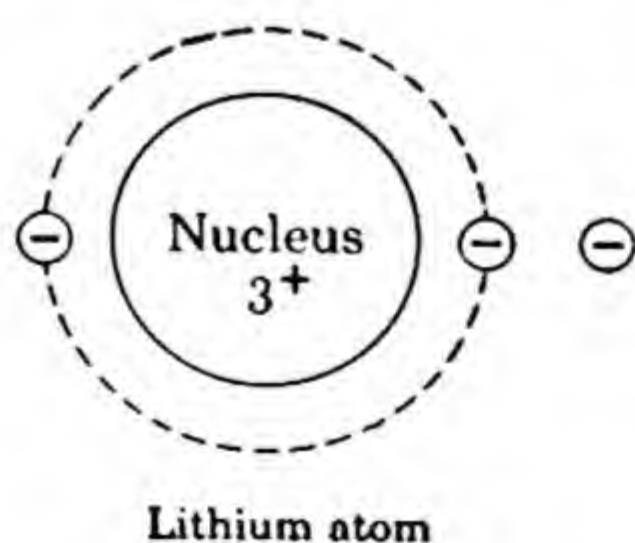
	Organic	Inorganic
Boiling point	Low	High
Melting point	Low	High
Solubility in water	Low	High
Conductivity of water solutions	Poor	Good
Solubility in organic solvents	High	Low
Speed of reactions	Slow	Fast

It should be noted that these differences are not to be regarded as completely general, but rather that they indicate tendencies. Exceptions to each can be found. Nevertheless, the great majority of the two types of compound can be said to conform with the table. The reason for these differences lies essentially in the types of valence exhibited by the two classes of compound. The typical inorganic compound is electrovalent, whereas the typical organic compound is covalent. Since both kinds of valence are to be found among inorganic compounds, familiar examples can be used to illustrate the differences in electrovalence and covalence.

The most striking fact about the combining power of the elements is their tendency toward developing a complete outer shell of electrons. For hydrogen, the complete outer shell contains two electrons; for the other elements of most interest in organic chemistry, the complete external shell contains eight electrons. The atoms strive to attain these numbers by losing electrons to, or gaining them from, other atoms or by sharing electrons with other atoms.

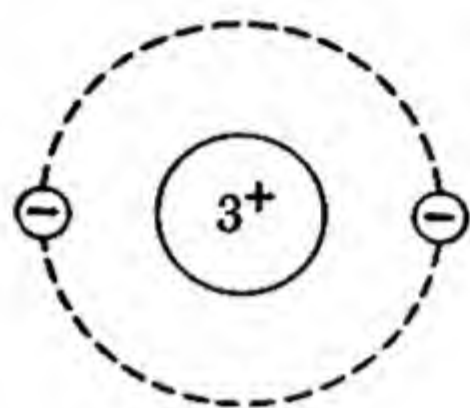
### ► ELECTROVALENCE

In electrovalence atoms lose or gain electrons. In lithium fluoride,  $\text{LiF}$ , there has been a loss of one electron by each lithium atom and a corresponding gain by each fluorine atom. In the neutral lithium atom there are three protons (as well as some neutrons) in the nucleus and three external electrons in two shells. The fluorine atom has

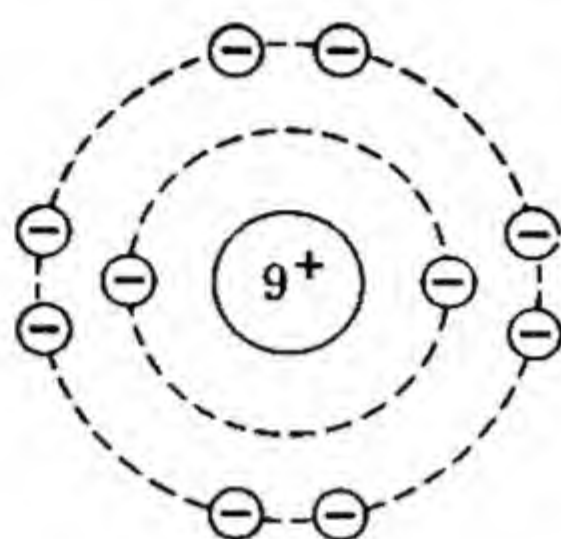




nine protons and nine electrons. It can be seen that lithium can most readily attain a complete outer shell (of two electrons) by the loss of an electron. On the other hand, fluorine can accomplish this end most readily by the gain of an electron which completes a shell of eight (octet). Therefore, these two elements combine to form the salt, lithium fluoride, by the complete transfer of an electron. It is to be observed that the lithium has attained a positive charge, since



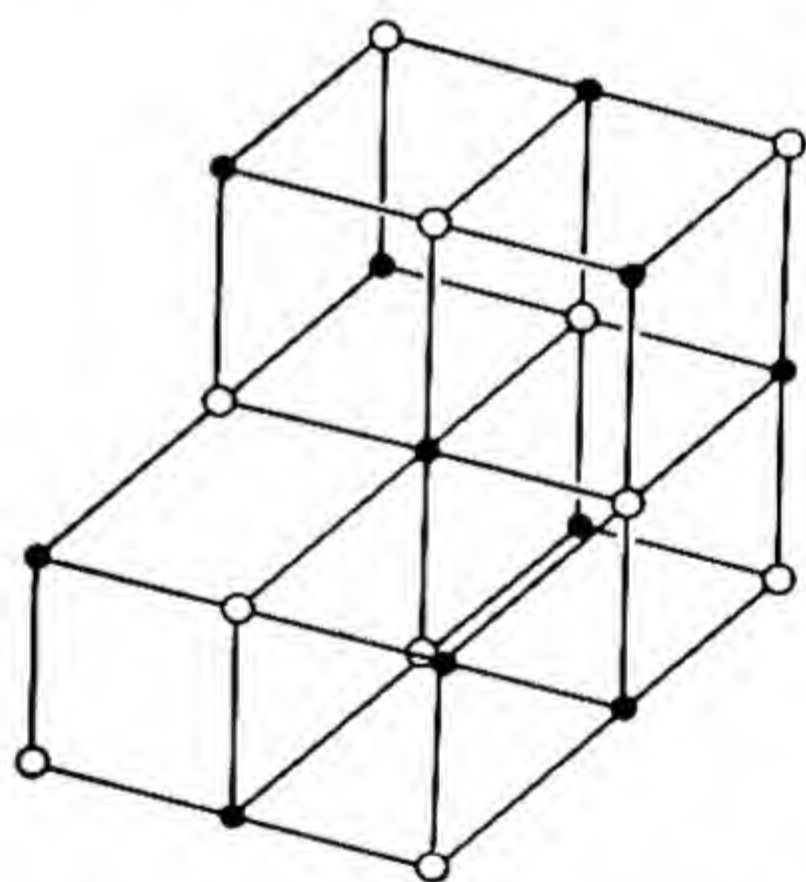
Lithium ion



Fluoride ion

it now has a deficiency of one electron. The fluorine is negatively charged, since it now has a surplus of one electron. It is to be noted further that the transfer has been *complete* and that the lithium is no longer associated with the electron it originally possessed. Such ions as lithium and fluoride having opposite electrical charges are attracted by each other; this attraction is not limited to the original partner in the combination but extends to any ion of opposite charge. Because of its obvious electrical nature this type of valence is called

The solid circles represent sodium ions and the open circles, chloride ions. Each is surrounded at equal distances by six ions of the opposite charge. There are strong electrical charges between the ions of opposite charge, but no one ion can be considered to be associated with any other ion.



A Portion of the Crystal Lattice of NaCl

electrovalence; the bond is said to be electrovalent, polar, or ionic. All salts, whether organic or inorganic, have bonds of this kind. In sodium chloride, for example, there has been a transfer of one electron

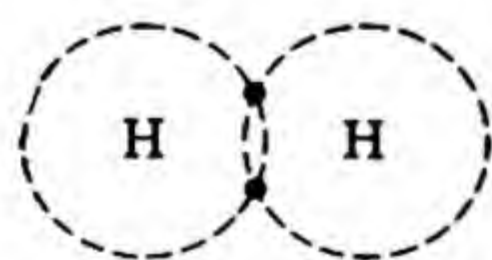


from sodium to chlorine, just as with sodium fluoride. In a salt such as magnesium chloride the situation is similar, but since the magnesium atom has two electrons in its outer shell it can complete the external shells of two chlorine atoms. The salt resulting can be pictured as  $\text{Mg}^{++} + 2\text{Cl}^{-}$ . In referring to the combining capacity of atoms in electrovalence we use algebraic signs (+ and -) which indicate whether the atoms can relinquish or accept electrons. Thus the valences of fluorine and chlorine are -1, those of sodium and lithium are +1, and that of magnesium +2.

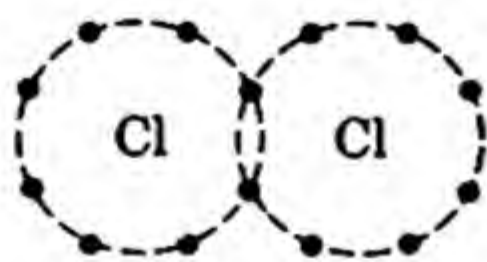
In a crystal of a salt each ion is surrounded by ions of opposite charge, the number depending on the type of crystal. Thus in sodium chloride each sodium atom is surrounded at equal distances by six chloride ions, and the converse is also true. In order to melt or vaporize a salt, the strong attractive forces which exist must be overcome, and as a consequence salts have very high melting and boiling points. The solution of salts in water is a process of dissociation of the ions already present in the crystal. Many reactions of salts in water involve ions of opposite charge. These reactions are very rapid because of the attraction of the ions for each other.

## ► COVALENCE

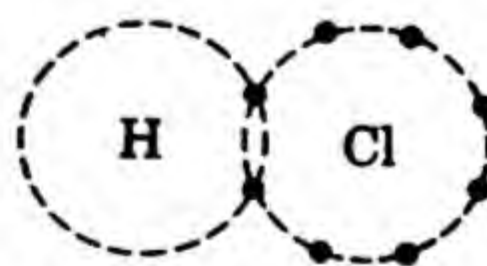
Covalence differs from electrovalence in that electrons are not transferred completely but are shared by the two atoms involved. This implies that it is possible for electrons to participate simultaneously as part of the outer shells of two atoms. The simplest example of covalence is met with in the hydrogen molecule, in which the two electrons (one from each atom) are associated with both atoms in the molecule. Thus the hydrogen molecule can be represented as in the following illustration. The chlorine molecule is another example. Each chlorine atom originally possesses seven external



Hydrogen



Chlorine



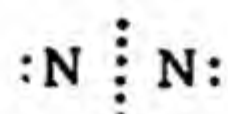
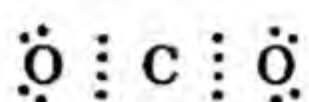
Hydrogen chloride

electrons, and, when two such atoms form a covalent bond, each atom supplies an electron to the linkage. As a result, each chlorine atom has eight electrons in its outer shell, of which two electrons are shared by both atoms. Such covalent bonds can exist between atoms of dif-

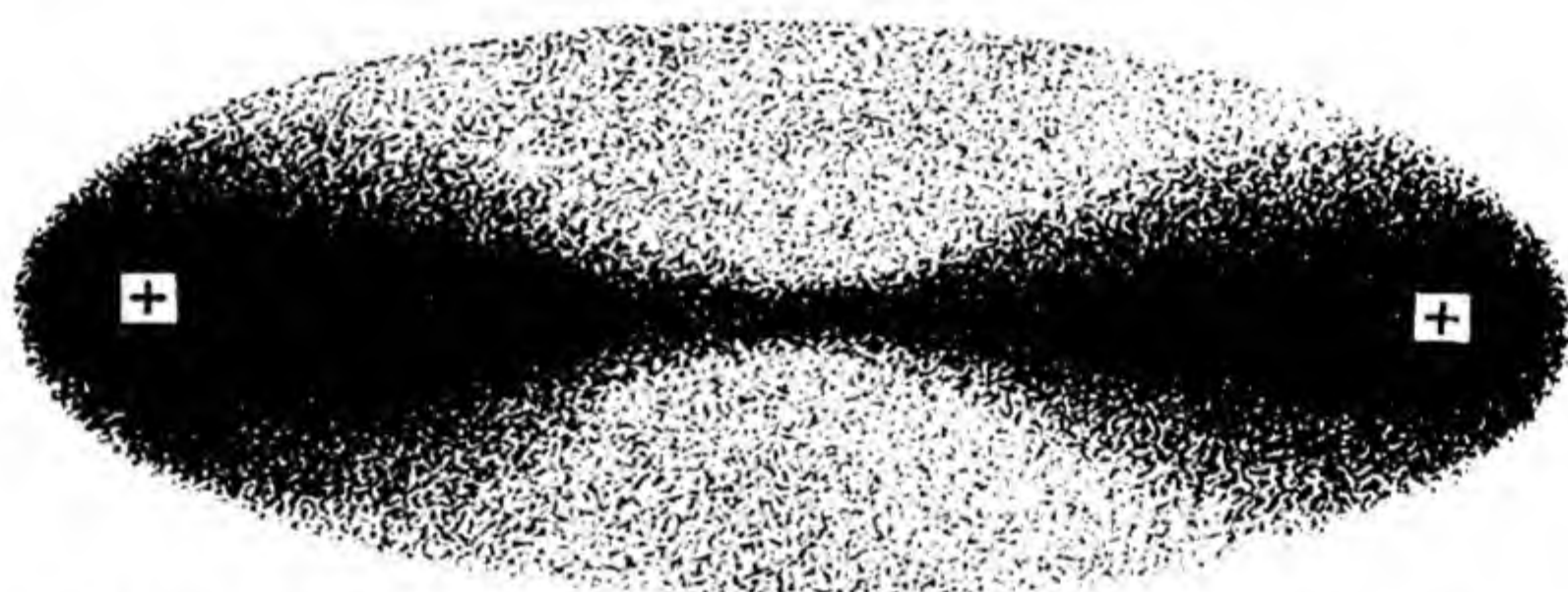


ferent kinds as well. The hydrogen-chlorine linkage is an example—each atom involved furnishes a single electron to the common bond, and each has a complete outer shell.

In the cases thus far mentioned the atoms involved in the covalent bonds have furnished single electrons. Instances are known in which the contribution of each atom to a bond is two or three electrons. In carbon dioxide, for example, each oxygen atom furnishes two electrons to its linkage with the carbon atom, and the carbon atom supplies two electrons to each of the two linkages. The result is that each atom has eight electrons in its outer shell. The nitrogen mole-



cule provides an example in which three electrons are furnished by each atom to the common linkage. Six electrons thus are shared by the two nitrogen atoms, and each possesses a pair of unshared electrons, so that the total in the external shell of each is eight.



*Electron Distribution in the Hydrogen Molecule*

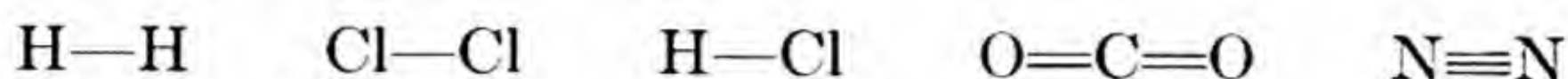
The darker the area, the greater the probability that an electron will be found there. The nuclei of the hydrogen atoms are located at the centers of the densest portions.

In the electronic formulas shown the electrons are pictured as occupying positions somewhere between the nuclei of the atoms concerned in the covalent bond. This is done merely for convenience. The electrons are not static, but in constant motion. As a result it is possible to make statements only about the probability that electrons are located in a certain volume, though the location between the nuclei is a favored one.

In writing the structural formulas for covalent compounds the electrons are not usually shown because for molecules having a large number of atoms electronic formulas would be unwieldy. Instead, a



convention is used in which a pair of shared electrons is represented by a short line and unshared electrons are not pictured. The covalent molecules just considered are represented thus:

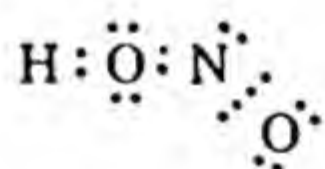


The linkages in the hydrogen molecule, the chlorine molecule, and hydrogen chloride are referred to as single bonds. Those in carbon dioxide are said to be double bonds, and that in the nitrogen molecule is a triple bond. The valences of the atoms involved are hydrogen, 1, chlorine, 1, carbon, 4, oxygen, 2, and nitrogen, 3. Note that no algebraic sign is attached to these numbers. The use of a positive or negative sign is not proper, since in forming the covalent bond electrons are merely shared, not lost or gained as they are in electrovalence.

In the crystal of a covalent compound the unit particles are molecules. There are no strong electrical forces to hold the crystal together, as with salts, and the intracrystalline forces are therefore more easily overcome. The melting and boiling points are thus much lower for purely covalent compounds than for salts. Reactions of covalent compounds in solution are slower than those of salts because contact of molecules is much more dependent upon random collisions, whereas oppositely charged ions attract each other.

### ► COORDINATE BONDS

A third type of valence, intermediate between electrovalence and covalence, is sometimes distinguished. It is most often met with in nitrogen compounds. The electronic structure of nitrous acid, a



Nitrous acid



Nitric acid

covalent compound, shows that all of the atoms have complete outer shells. However, the nitrogen atom has a pair of unshared electrons which it can share with another atom. It does so in nitric acid. The new nitrogen-oxygen bond is covalent in the sense that the electrons constituting it are shared. This bond also has some ionic character, for an oxygen atom is electrically neutral, and the new oxygen atom in nitric acid acquires some negative charge, since it gains a share in the two electrons supplied by the nitrogen atom.

Such a bond is called “semipolar” or “coordinate” and is represented in structural formulas in one of two ways, as illustrated by the formulas for nitric acid. The arrow is meant to indicate that the



nitrogen has contributed both electrons to the linkage, and, in general, it points away from the donor toward the acceptor atom. In the other formula the representation is meant to indicate that the bond is partially covalent and partially ionic.



# *Methane and its derivatives*



The model of methane shows that the molecule is nonplanar. The dark central portion is the carbon atom. Surrounding it and equidistant from each other are the four hydrogen atoms. Lines connecting the centers of all the hydrogen atoms would outline a regular tetrahedron.

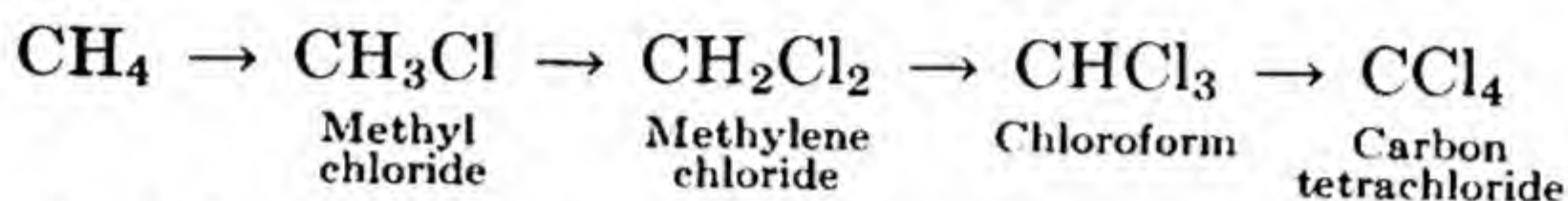
Compounds containing only hydrogen and carbon, as stated earlier, are known as hydrocarbons, and all other organic compounds can be considered to be derivatives of them. The simplest hydrocarbon is methane,  $\text{CH}_4$ , which is one of a series of hydrocarbons called paraffins that are grouped together because of similar chemical properties. The paraffins are said to be *saturated* because they contain only single bonds. Compared to other types of hydrocarbons, the paraffins are unreactive. For example, unless conditions are extreme, reagents such as hydrochloric acid, sulfuric acid, metallic sodium, and potassium permanganate have no effect upon them.

Methane is a compound of very wide occurrence. It is the chief constituent of natural gas and can be found in coal mines and in the atmospheres of the outer planets of the solar system. It is produced also by microorganisms in various fermentation processes. Methane occurs in marsh gas and is also produced in the tanks of sewage disposal plants and in the rumen of dairy cattle.

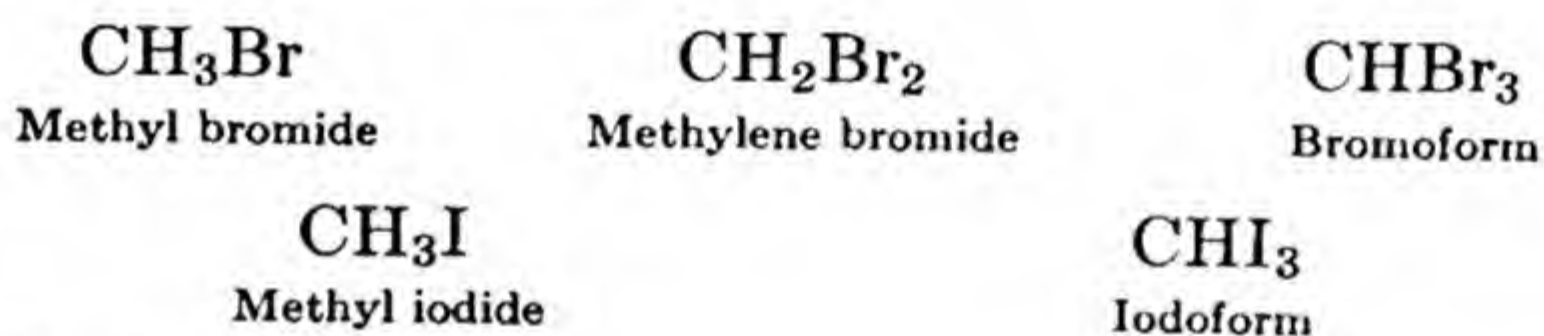


## ► HALOGEN DERIVATIVES OF METHANE

Since methane is saturated, it can undergo chemical reaction only by replacement of hydrogen by another atom or group. Such a reaction—the replacement of hydrogen—is known as a *substitution* reaction. When the entering group is a halogen the reaction is *halogenation*. The replacement of one or more of the hydrogen atoms in methane by chlorine can be brought about by heating a mixture of methane and chlorine or by exposure to a strong light. The reaction is a difficult one to control, and the four chlorinated derivatives which result differ in the amount of chlorine they contain:



Bromination of methane also leads to a mixture of four compounds. Iodine, the least reactive of the common halogens, shows little tendency to iodinate saturated hydrocarbons. Nevertheless, iodine derivatives of methane can be prepared by other procedures and are well known. The formulas and names of some of the bromine and iodine derivatives of methane are



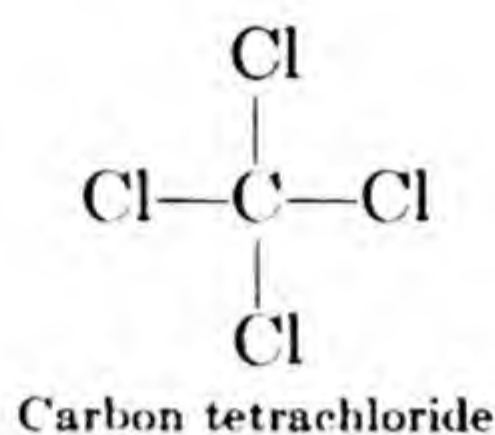
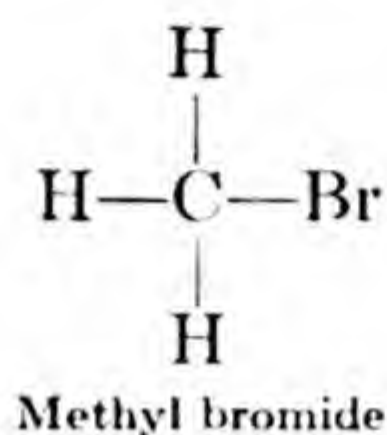
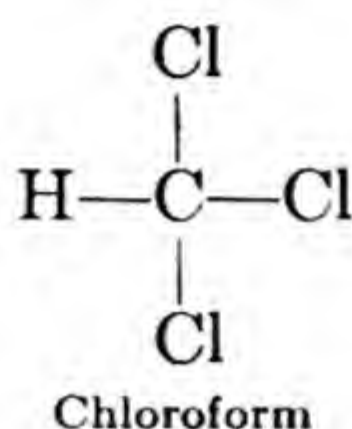
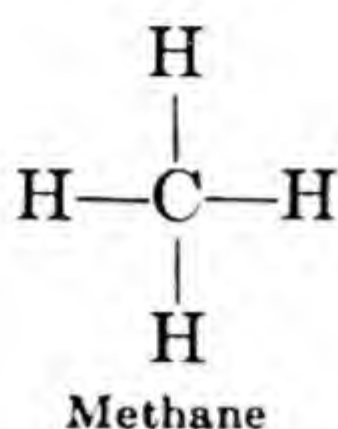
## ► FORMULAS

All of the hydrogen atoms in methane are equivalent and are situated at positions equidistant from each other in space. They therefore have the same relation to one another as the apexes of a tetrahedron. Carbon is often referred to as a *tetrahedral* atom, meaning that the four valences are directed to the apexes of a regular tetrahedron, the center of which is also the center of the carbon atom. The following figure shows the positions of the hydrogen atoms in methane; the dotted lines connecting the hydrogen atoms outline a regular tetrahedron.



Because of the difficulty of representing three-dimensional formulas on paper the space formulas are not often used. It is generally more

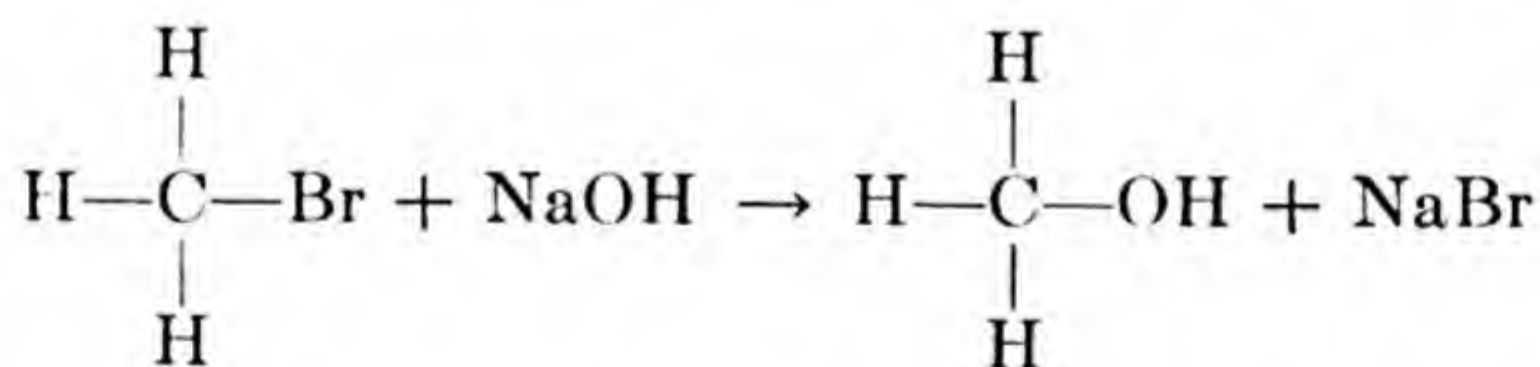
convenient to employ these simplified formulas as abbreviations for the three-dimensional formulas.



Often formulas of this kind are condensed still further. Thus the four compounds given would be represented  $\text{CH}_4$ ,  $\text{CHCl}_3$ ,  $\text{CH}_3\text{Br}$ ,  $\text{CCl}_4$ . No bonds are shown in such condensed structural formulas.

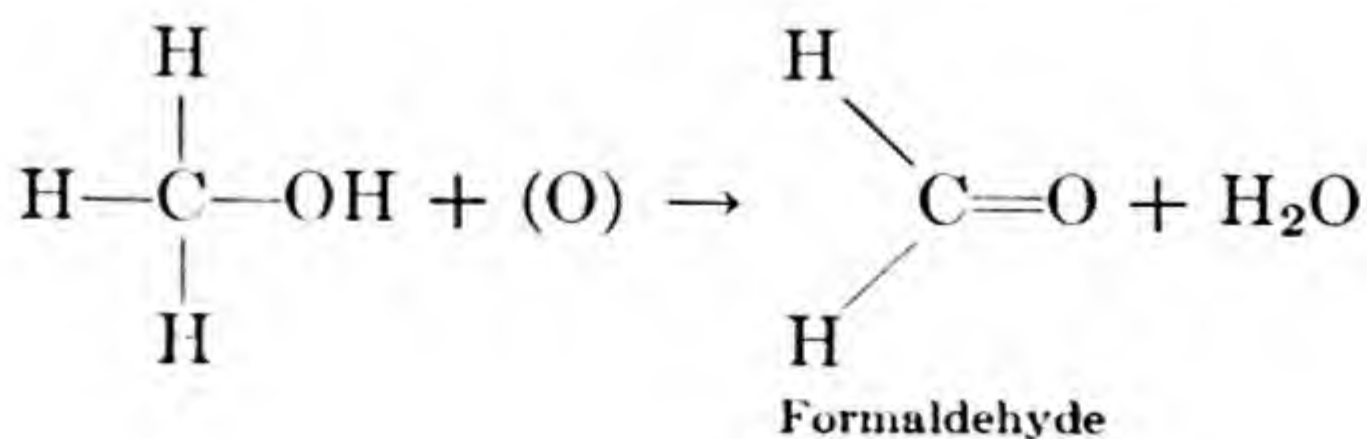
### ► OXYGEN DERIVATIVES OF METHANE

If methyl bromide (or other methyl halide) is heated with aqueous sodium hydroxide, the halogen is replaced by a hydroxyl group. The new compound is called methyl alcohol, and the hydroxyl group



(—OH) is typical of a large number of compounds called alcohols. Such a group, characteristic of a series of compounds and responsible for the typical reactions of the series, is said to be the *functional group* of the series.

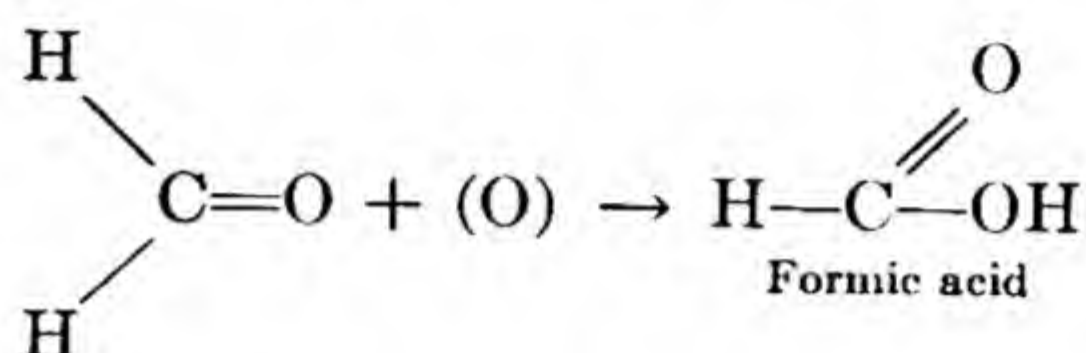
If methyl alcohol is oxidized carefully, it is converted into formaldehyde.





In this process the hydroxyl group of the alcohol is transformed into a carbonyl group  $\left( \begin{array}{c} \diagup \\ \text{C}=\text{O} \\ \diagdown \end{array} \right)$ . Formaldehyde therefore has chemical properties different from those of methyl alcohol.

Further oxidation changes formaldehyde into formic acid:

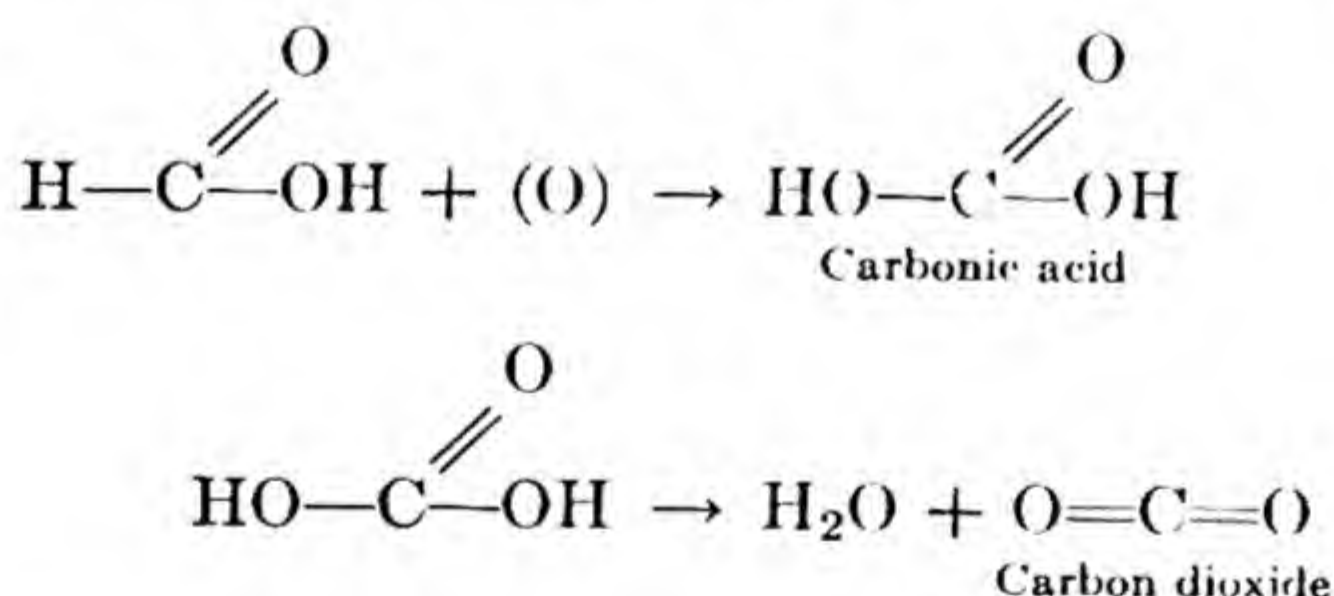


In this reaction the carbonyl group is transformed into another func-

tional group,  $\overset{\overset{\text{O}}{\parallel}}{\text{C}}-\text{OH}$ , known as the carboxyl group. Formic acid was first obtained from ants, and its name is derived from the Latin word for ant (*formica*).

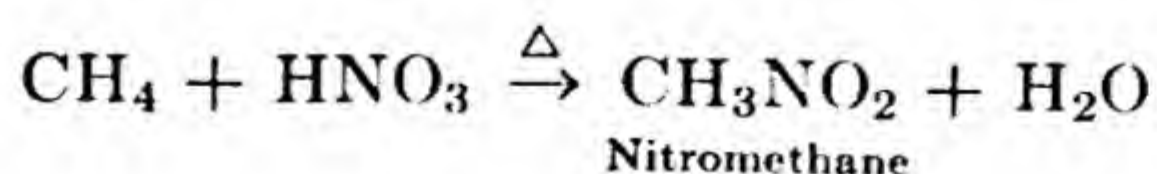
In these oxidations it should be noted that the valence of carbon remains unchanged at 4; the oxidation proceeds either by addition of oxygen to the molecule or by removal of hydrogen from it.

Oxidation of formic acid gives carbonic acid, which, like most compounds containing two hydroxyl groups on the same carbon atom, is unstable. It decomposes into carbon dioxide and water.

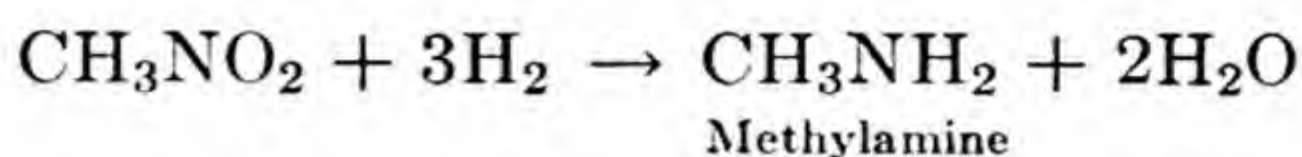


## ► NITROGEN DERIVATIVES OF METHANE

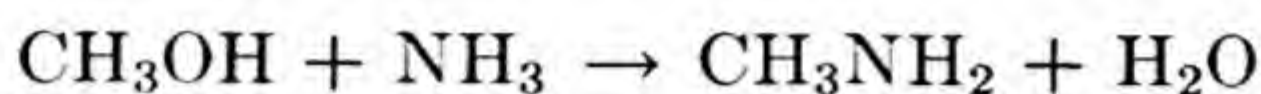
When methane is treated with nitric acid at high temperatures one of the hydrogen atoms is replaced by  $-\text{NO}_2$ , known as the nitro group. The reaction is an example of *nitration*, and the product is called nitromethane.



Reduction of nitromethane changes the nitro group to  $\text{—NH}_2$ , or the amino group. The compound produced is called methylamine.



Methylamine may be regarded as a derivative of ammonia; in fact, it is usually made by heating ammonia with methyl alcohol.



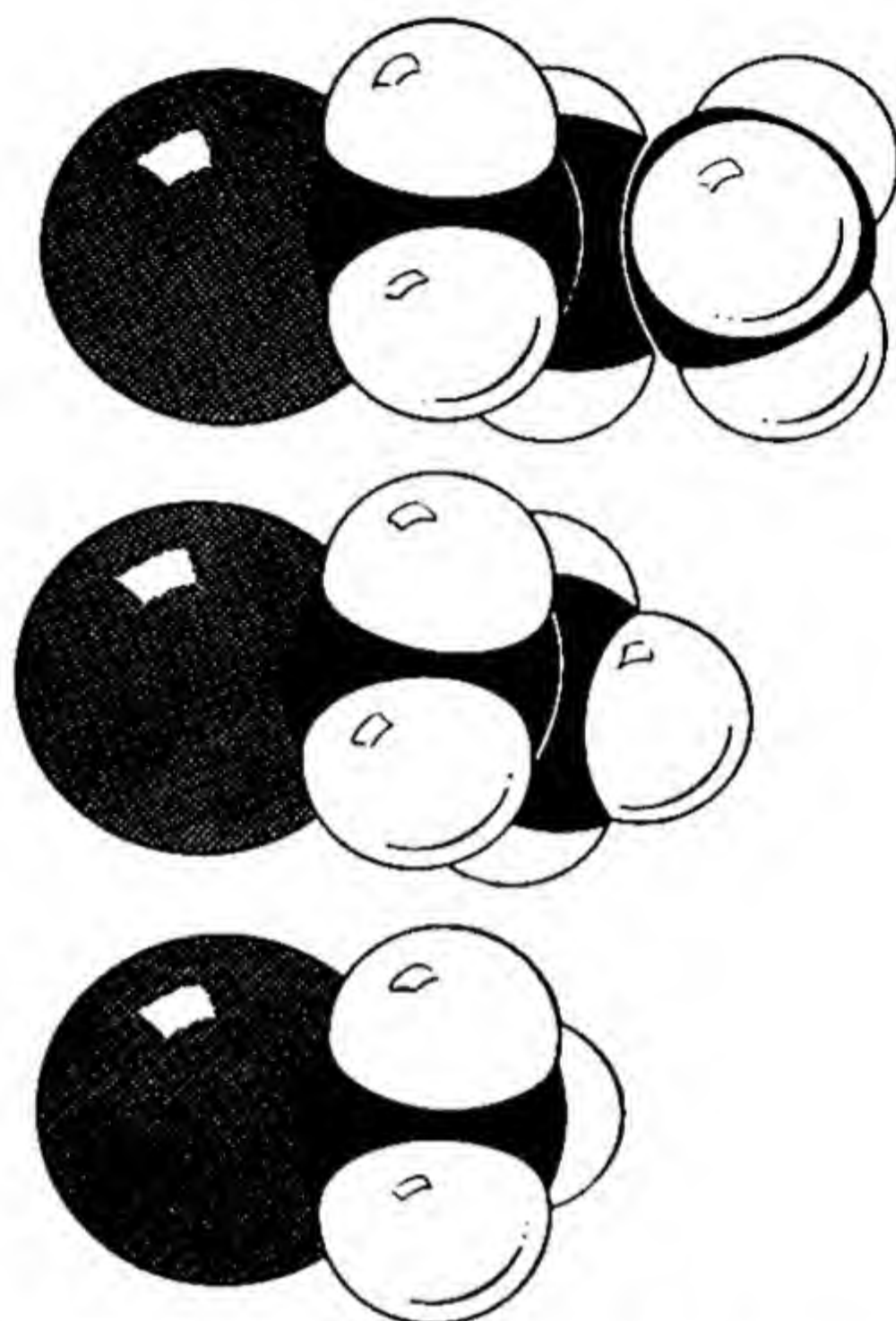
Replacement of the hydroxyl by the amino group is possible also in

acids. The carboxyl group is thus changed to  $\text{—}\overset{\text{O}}{\parallel}{\text{C}}\text{—NH}_2$ , known as the amide group. Formic acid, for example, yields formamide.

## ► QUESTIONS ---

1. Write structural formulas for methylamine, nitromethane, carbon tetrabromide, and methylene iodide.
2. Write electronic formulas for formaldehyde and for methylene chloride.
3. Only one compound of the formula  $\text{CH}_2\text{Cl}_2$  is known. If the carbon atom were planar, instead of tetrahedral, more than one structure would be possible. Explain.





The models show the first three examples in the homologous series of the alkyl iodides: methyl iodide,  $\text{CH}_3\text{I}$ , ethyl iodide,  $\text{CH}_3\text{CH}_2\text{I}$ , and *n*-propyl iodide,  $\text{CH}_3\text{CH}_2\text{CH}_2\text{I}$ . The iodine atom, common to all compounds of the series, is the reactive part of the molecule and is responsible for the typical reactions of the series.

We have seen in Chapter 2 that various compounds can be derived from methane by appropriate reactions. It was mentioned further that methane is a representative of a series of compounds known as paraffins. Other members of this series are ethane, whose molecular formula is  $\text{C}_2\text{H}_6$ , propane,  $\text{C}_3\text{H}_8$ , and butane,  $\text{C}_4\text{H}_{10}$ . In-



# Homologous Series

Number of Carbon Atoms

Name	1	2	3	4	5	Functional Group	General Formula
Paraffins	$\text{CH}_4$ Methane	$\text{C}_2\text{H}_6$ Ethane	$\text{C}_3\text{H}_8$ Propane	$\text{C}_4\text{H}_{10}$ Butane	$\text{C}_5\text{H}_{12}$ Pentane		$\text{C}_n\text{H}_{2n+2}$ or $\text{RH}$
Alkyl halides	$\text{CH}_3\text{X}$ Methyl halide	$\text{C}_2\text{H}_5\text{X}$ Ethyl halide	$\text{C}_3\text{H}_7\text{X}$ Propyl halide	$\text{C}_4\text{H}_9\text{X}$ Butyl halide	$\text{C}_5\text{H}_{11}\text{X}$ Amyl halide	$-\text{X}'$	$\text{C}_n\text{H}_{2n+1}\text{X}$ or $\text{RX}$
Alcohols	$\text{CH}_3\text{OH}$ Methyl alcohol	$\text{C}_2\text{H}_5\text{OH}$ Ethyl alcohol	$\text{C}_3\text{H}_7\text{OH}$ Propyl alcohol	$\text{C}_4\text{H}_9\text{OH}$ Butyl alcohol	$\text{C}_5\text{H}_{11}\text{OH}$ Amyl alcohol	$-\text{OH}$	$\text{ROH}$
Aldehydes	$\text{HC}=\text{O}$ Formaldehyde	$\text{CH}_3\text{C}=\text{O}$ Acetaldehyde	$\text{C}_2\text{H}_5\text{C}=\text{O}$ Propionaldehyde	$\text{C}_3\text{H}_7\text{C}=\text{O}$ Butyraldehyde	$\text{C}_4\text{H}_9\text{C}=\text{O}$ Valeraldehyde	$\text{O}=\text{C}-\text{H}$	$\text{RC}=\text{O}$ $\text{H}$
Acids	$\text{HC}=\text{O}$ Formic acid	$\text{CH}_3\text{C}=\text{O}$ Acetic acid	$\text{C}_2\text{H}_5\text{C}=\text{O}$ Propionic acid	$\text{C}_3\text{H}_7\text{C}=\text{O}$ Butyric acid	$\text{C}_4\text{H}_9\text{C}=\text{O}$ Valeric acid	$\text{O}=\text{C}-\text{OH}$	$\text{RC}=\text{O}$ $\text{OH}$
Amides	$\text{HC}=\text{O}$ Formamide	$\text{CH}_3\text{C}=\text{O}$ Acetamide	$\text{C}_2\text{H}_5\text{C}=\text{O}$ Propionamide	$\text{C}_3\text{H}_7\text{C}=\text{O}$ Butyramide	$\text{C}_4\text{H}_9\text{C}=\text{O}$ Valeramide	$\text{O}=\text{C}-\text{NH}_2$	$\text{RC}=\text{O}$ $\text{NH}_2$
Nitro compounds	$\text{CH}_3\text{NO}_2$ Nitromethane	$\text{C}_2\text{H}_5\text{NO}_2$ Nitroethane	$\text{C}_3\text{H}_7\text{NO}_2$ Nitropropane	$\text{C}_4\text{H}_9\text{NO}_2$ Nitrobutane	$\text{C}_5\text{H}_{11}\text{NO}_2$ Nitropentane	$-\text{NO}_2$	$\text{RNO}_2$
Amines	$\text{CH}_3\text{NH}_2$ Methylamine	$\text{C}_2\text{H}_5\text{NH}_2$ Ethylamine	$\text{C}_3\text{H}_7\text{NH}_2$ Propylamine	$\text{C}_4\text{H}_9\text{NH}_2$ Butylamine	$\text{C}_5\text{H}_{11}\text{NH}_2$ Amylamine	$-\text{NH}_2$	$\text{RNH}_2$



spection reveals that as we ascend the series the formulas of the paraffins increase by  $\text{CH}_2$ , and this enables us to write a *general formula* for the paraffins,  $\text{C}_n\text{H}_{2n+2}$ . The substitution of any whole number for  $n$  in this formula gives the proper number of carbon and hydrogen atoms. Thus a twenty-carbon paraffin would be  $\text{C}_{20}\text{H}_{42}$ . Such a series as the paraffins in which the compounds have similar properties and in which succeeding members differ by the same increment is said to be a *homologous series*. The members of the series are spoken of as *homologs* of each other.

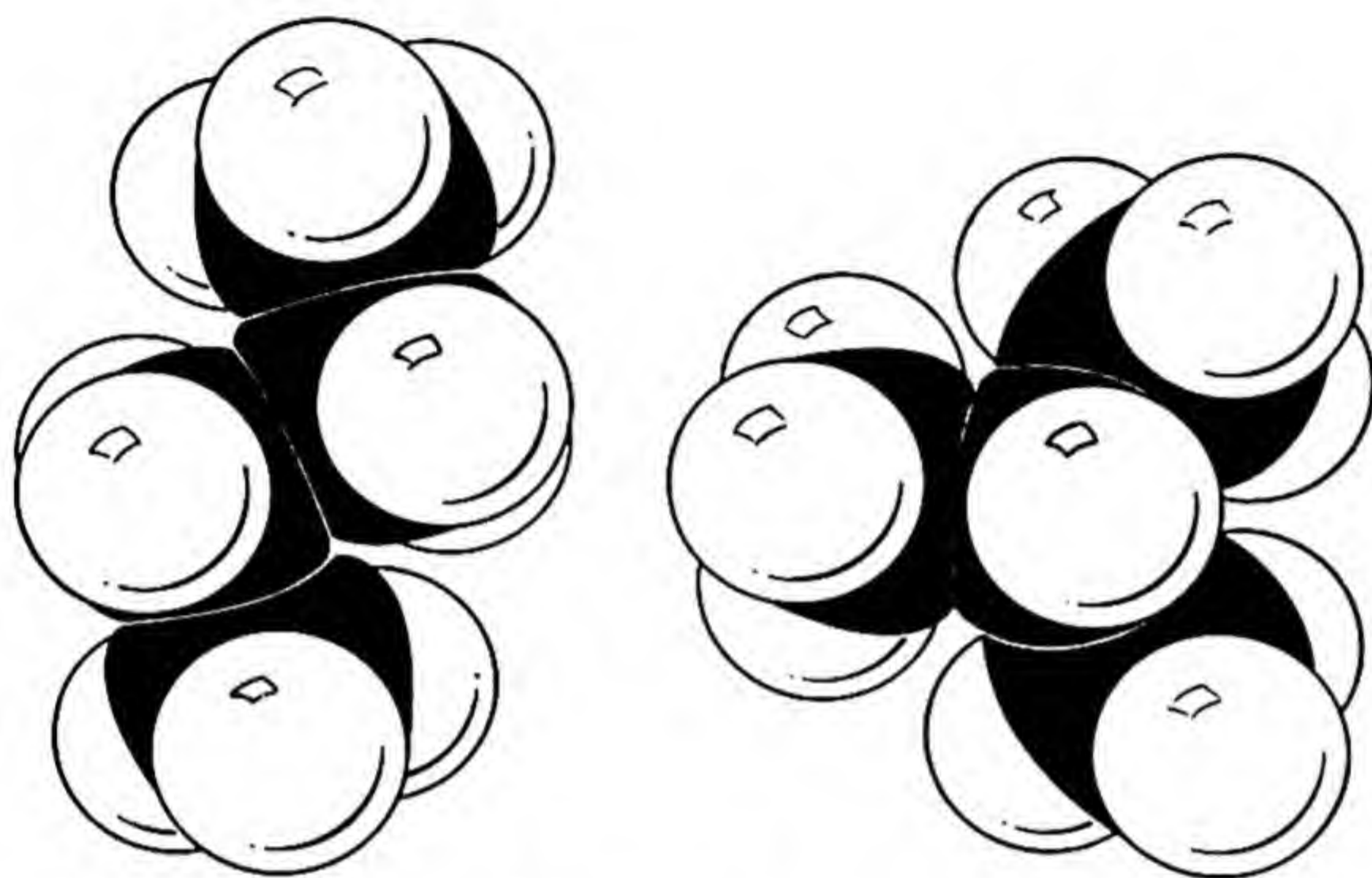
As methane is the first member of the paraffins, so methyl chloride is the first member of a series called *alkyl chlorides*, the general formula of which is  $\text{C}_n\text{H}_{2n+1}\text{Cl}$ . Substituting integers for  $n$  gives the molecular formulas  $\text{CH}_3\text{Cl}$ ,  $\text{C}_2\text{H}_5\text{Cl}$ ,  $\text{C}_3\text{H}_7\text{Cl}$ ,  $\text{C}_4\text{H}_9\text{Cl}$ , etc. The groups attached to the chlorine atom can be written generally as  $\text{C}_n\text{H}_{2n+1}$  and are known as *alkyl groups*. Because alkyl groups are of such frequent occurrence in organic chemistry it is usual to abbreviate their general formula to "R," and thus alkyl chlorides are often represented as  $\text{RCl}$ . Similar homologous series are known for the other halogens. The general formulas are  $\text{C}_n\text{H}_{2n+1}\text{Br}$  ( $\text{RBr}$ ) and  $\text{C}_n\text{H}_{2n+1}\text{I}$  ( $\text{RI}$ ). The alkyl chlorides, bromides, and iodides have similar properties, and it is found convenient to write a general formula ( $\text{RX}$ ) for them. The symbol  $\text{X}$  is used in organic chemistry to represent any halogen, and the symbol  $\text{RX}$  represents any *alkyl halide*.

In like manner there exist homologous series for all of the derivatives of methane mentioned in Chapter 2, and general formulas can be written for each of these series.

## ► QUESTIONS

1. The nitriles constitute a homologous series, the first three members of which are  $\text{HCN}$ ,  $\text{CH}_3\text{CN}$ ,  $\text{C}_2\text{H}_5\text{CN}$ . Write the next two members of the series and a general formula for the nitriles.

2. The olefins constitute a series of hydrocarbons, the first three members of which are  $\text{C}_2\text{H}_4$ ,  $\text{C}_3\text{H}_6$ ,  $\text{C}_4\text{H}_8$ . Write the next two members and the general formula for the series. Would it be legitimate to substitute  $n = 1$  in this formula? Explain.

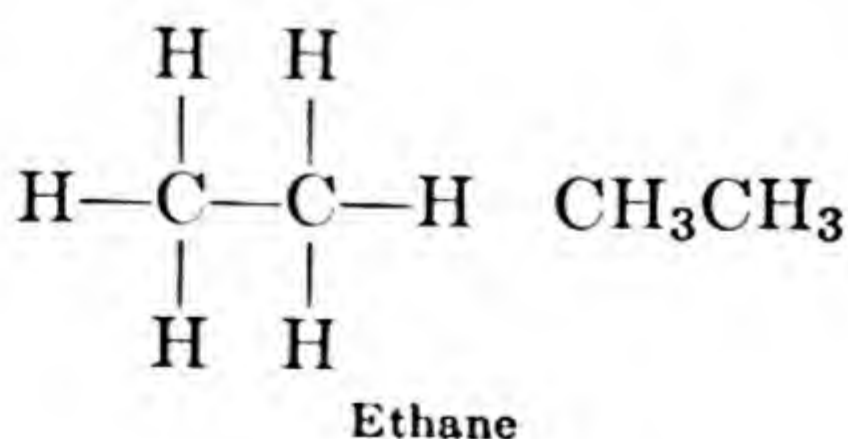
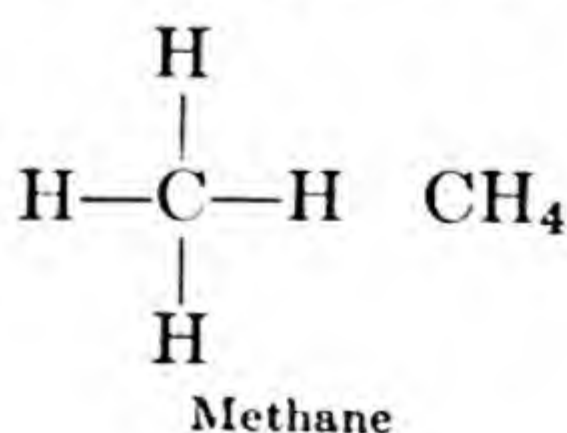


The phenomenon of isomerism pervades the entire field of organic chemistry. The models show the isomers butane,  $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_3$ , and isobutane,  $\text{CH}_3\text{CHCH}_3$ . The mo-

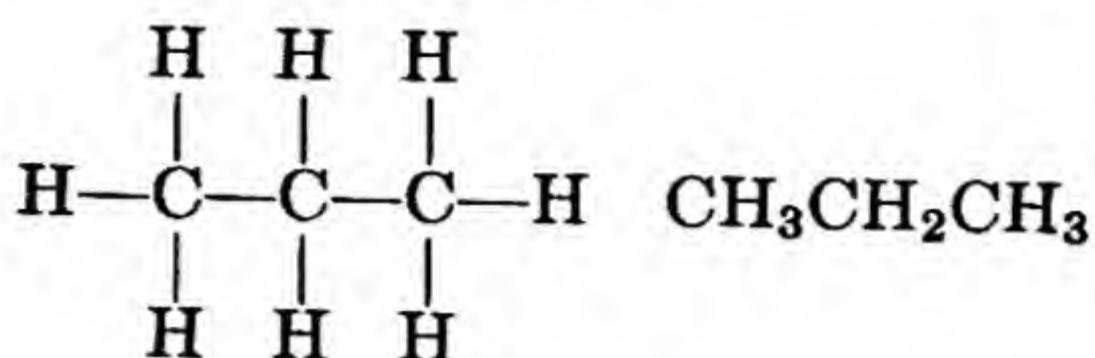
lecular formula of both is  $\text{C}_4\text{H}_{10}$ . The differences in structure of the two isomers are well shown by the models. The straight chain in butane and the branched chain in its isomer give the two molecules entirely different shapes.

## ► PARAFFINS

**Isomerism.** The structural formulas for the first three members of the paraffin series are

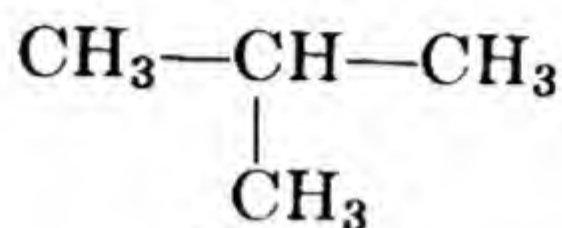






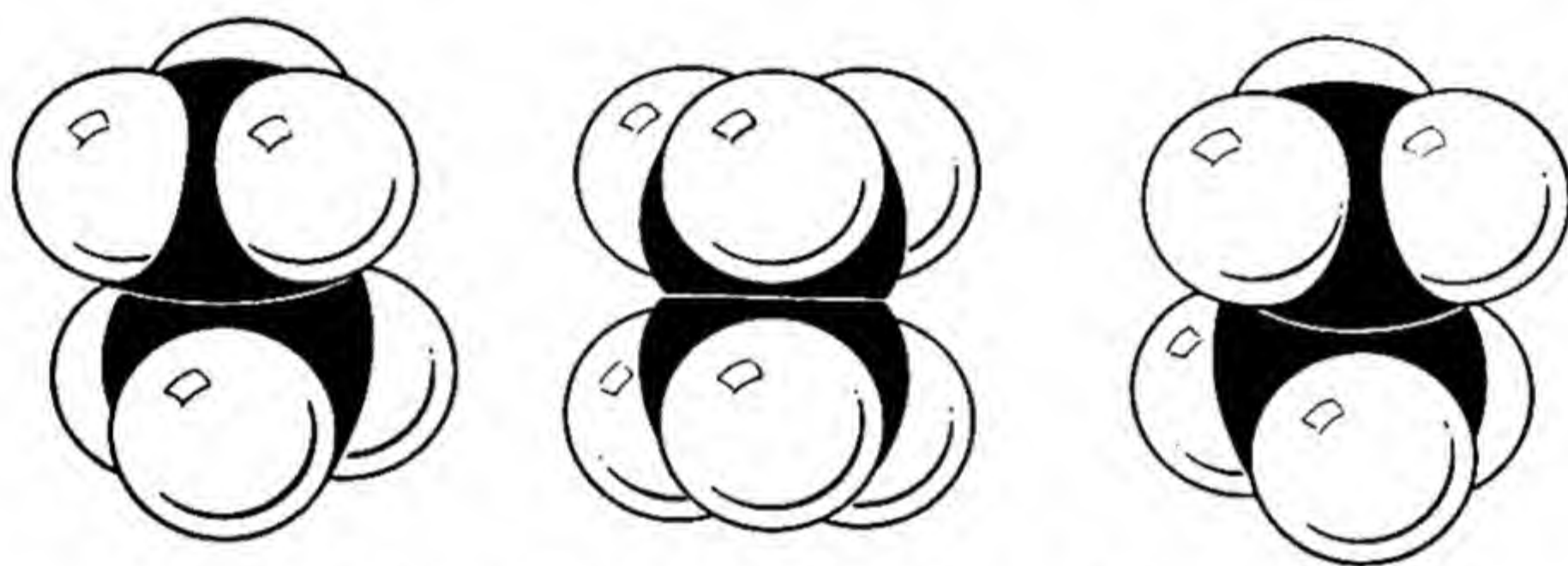
Propane

When an attempt to write a structural formula for butane is made it is discovered that there are two possible formulas which can be written.

*n*-Butane

Isobutane

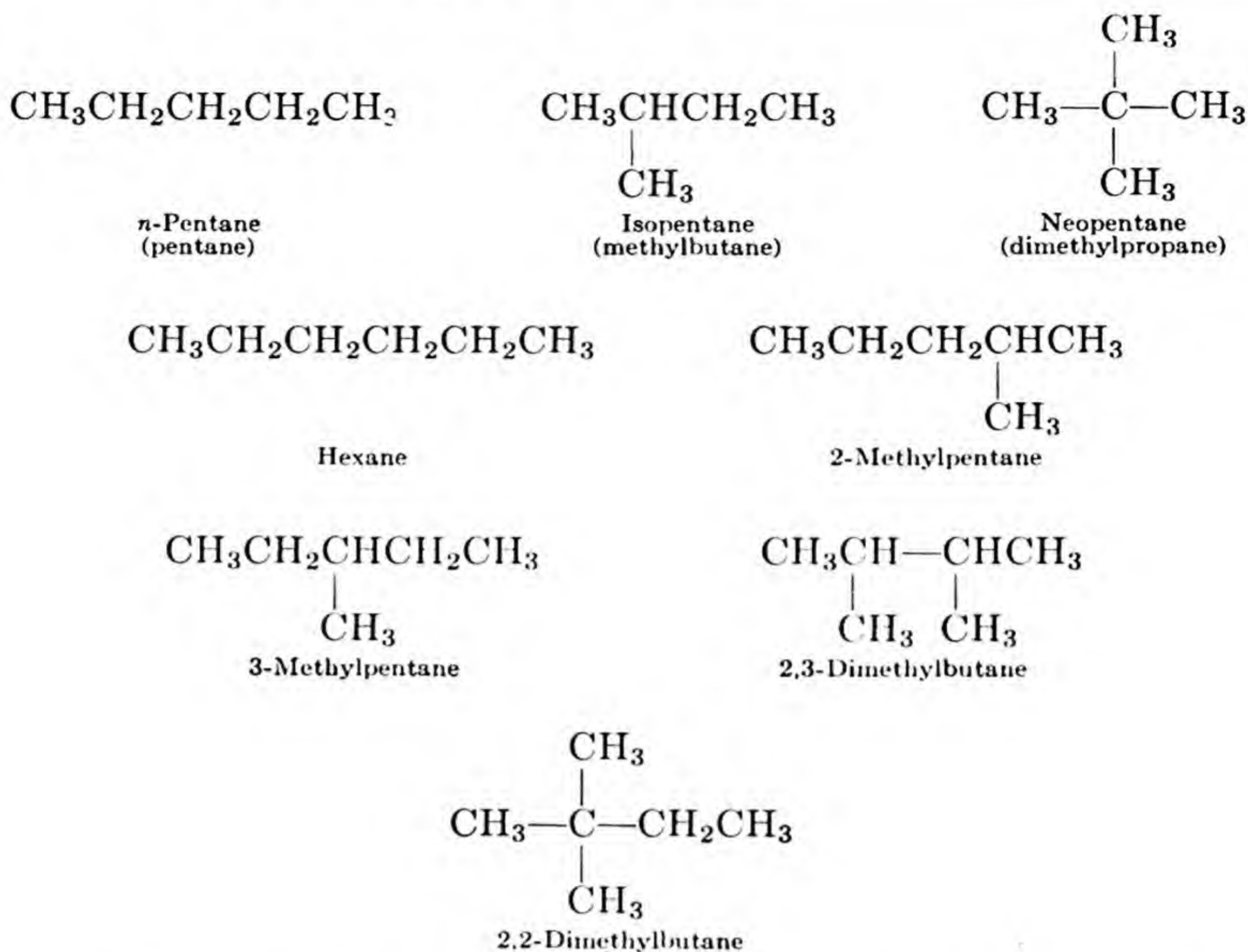
These formulas represent different structures, for, as can be seen, in isobutane there are three methyl groups attached to a central carbon atom. Other points of difference can be discerned by inspection.

*Conformations of the Ethane Molecule*

Because of the tetrahedral nature of the carbon atom, it might seem that isomers should occur because of the placement of the atoms in space. The nearly free rotation about most carbon-carbon bonds, however, renders these possible conformations interconvertible. Thus only one ethane exists, though an infinite number of conformations are possible.

tion of the two formulas. *n*-Butane ("normal" butane) and isobutane are different compounds, for, though their properties are similar, differences can be measured. Thus *n*-butane boils at 0° and isobutane at -10°. Compounds such as these, having identical molecular formulas but differing in structure, are called *isomers*. The phenomenon is called *isomerism*. It is very common among all kinds of organic compounds, less so among inorganic substances. The possibility of isomerism increases with the complexity of a molecule. Thus there are three isomeric pentanes, C<sub>5</sub>H<sub>12</sub>, and five hexanes, C<sub>6</sub>H<sub>14</sub>.





It is possible to calculate the number of isomers for a given molecular formula. Thus there are nine heptanes ( $\text{C}_7\text{H}_{16}$ ), 355 possible dodecanes ( $\text{C}_{12}\text{H}_{26}$ ), and over 60 trillion possible tetracontanes ( $\text{C}_{40}\text{H}_{82}$ ). Obviously not all of the dodecanes or tetracontanes are known compounds, but in cases in which it has been feasible to test the prediction the number of isomers predicted and the number actually isolated have always been found to be the same.

**Nomenclature.** The phenomenon of isomerism has made the problem of assigning a distinctive name to each compound a difficult one. This problem was recognized rather early in the history of organic chemistry, and in 1894 a group of chemists meeting in Geneva evolved a systematic method which is known commonly as the Geneva system, although later conventions of the International Union of Chemistry (I.U.C.) in other cities modified the rules somewhat. The essentials of the system are given here, with some comment.

1. *The names in each homologous series shall have a characteristic ending.* Endings were made to conform as much as possible to previous usage. Thus "ane" is the ending for paraffins.

2. *The root of the name shall be determined by the longest carbon chain.* Here also syllables as nearly like those in previous use were



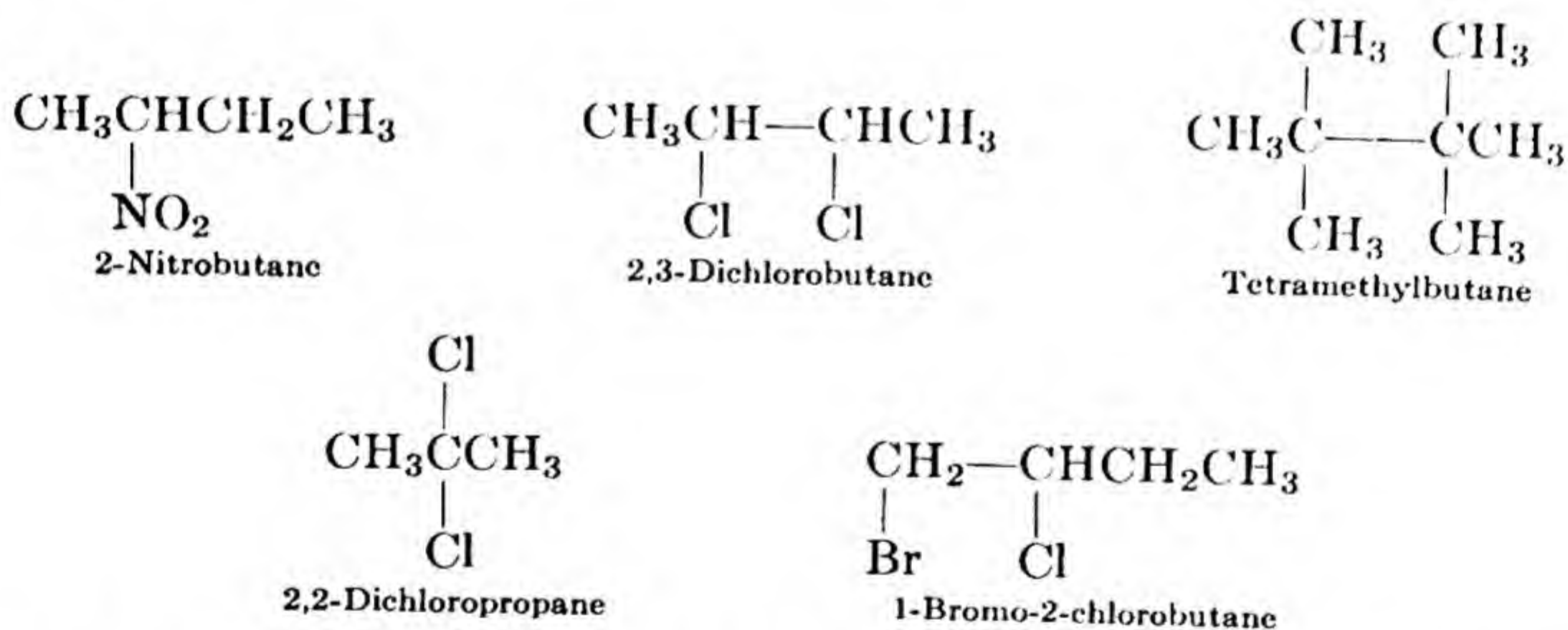
selected. Those employed were meth- (1), eth- (2), prop- (3), but- (4), pent- (5), hex- (6), hept- (7), oct- (8). Higher members have roots derived from Greek and Latin.

3. *Substituent atoms or groups shall be indicated by prefixes.* The commoner groups handled in this way are the halogens, the alkyl groups, and the nitro group.

4. *When necessary, the carbon atoms in the longest chain shall be numbered consecutively for the purpose of locating substituent groups. The numbering shall be done in the direction which makes the locating numbers as small as possible.* This is necessary so that each substance may have a distinctive name.

It should be noted that simpler compounds and those occurring naturally are often referred to by unsystematic names. Often the reason is historical, the compound having been known by the name before the system was devised. Occasionally the structure of a compound is unknown, and it is impossible to use systematic nomenclature. Names accorded such compounds often remain in use even after the structures have been determined.

A few systematic and trivial names have already been given for the pentanes and hexanes. Further examples of systematic nomenclature are

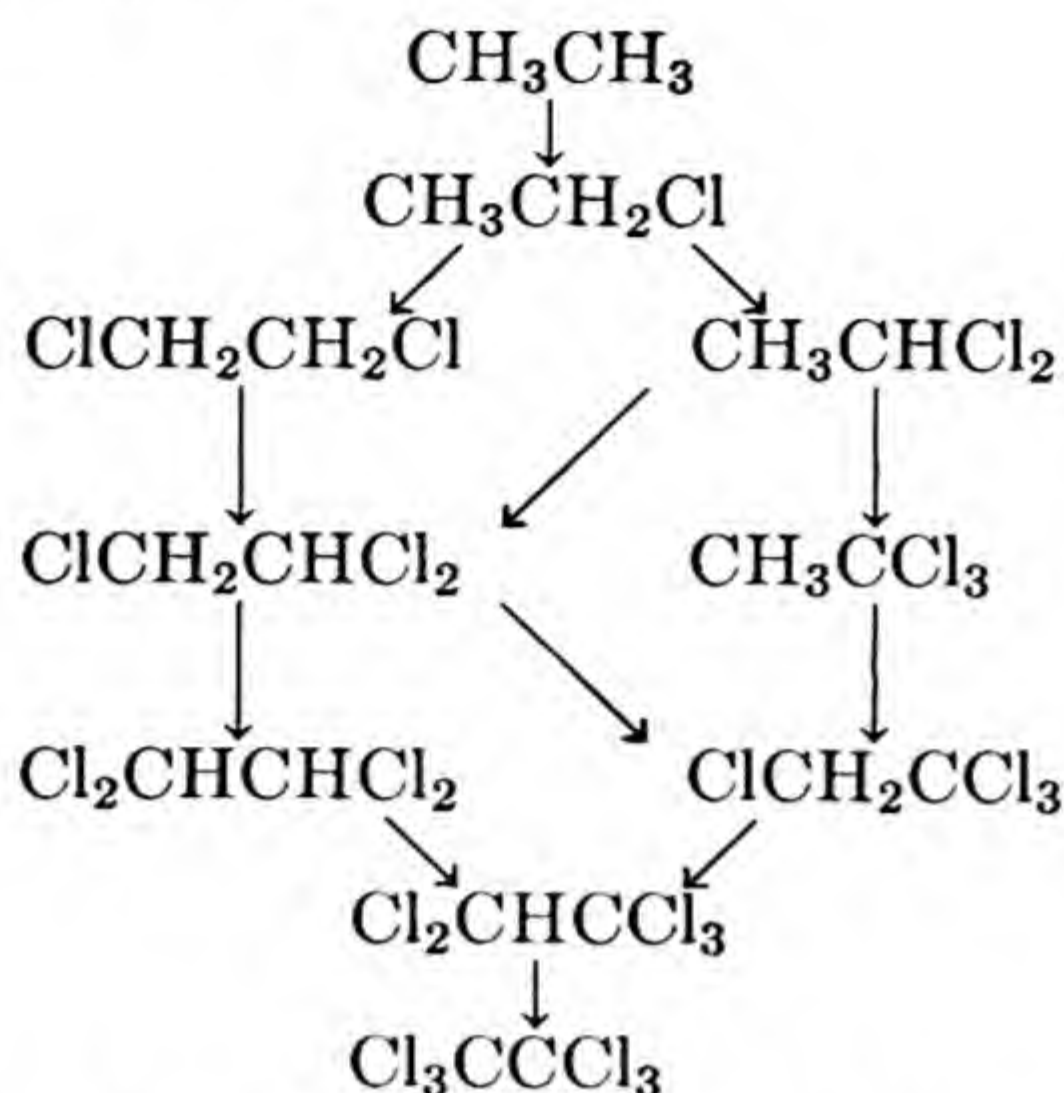


Note that locating numbers are assigned to all substituents even though they may be attached to the same carbon atom. When two or more groups of the same kind are substituents the prefixes di-, tri-, tetra-, penta-, etc., are introduced to cut down the length of the name. If only one substituent of a type is present, no such prefix is used.

**Reactions of Paraffins.** All paraffins undergo halogenation in the same fashion as methane. With ethane, for example, chlorination

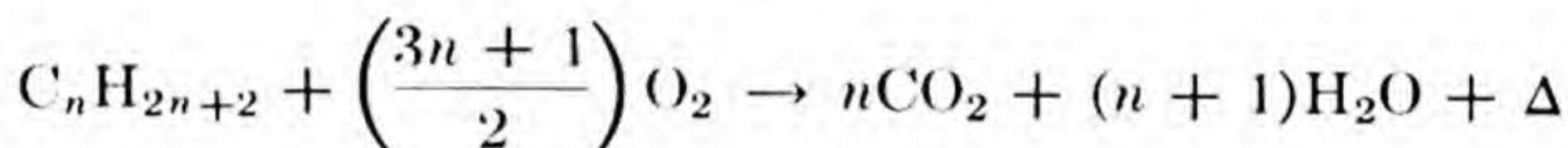
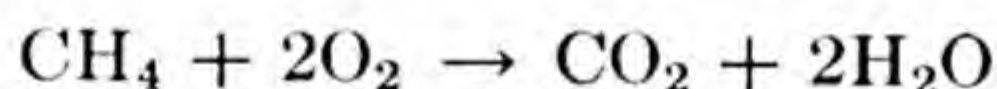


can take the following course:



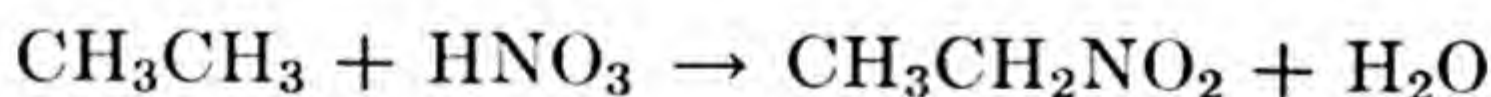
Hydrogen chloride is formed in each step of the substitution process. As with methane, the chlorination is difficult to control, since each substitution is of about the same order of difficulty.

All the paraffin hydrocarbons burn, and if combustion is complete the products are carbon dioxide and water.



A considerable amount of heat is evolved in these reactions, which makes them useful as sources of energy. Gasoline, diesel fuel, butane, and natural gas are burned for this purpose.

A reaction of commercial importance is the nitration of the lower paraffins at high temperatures. Ethane, for example, yields nitroethane along with other products.

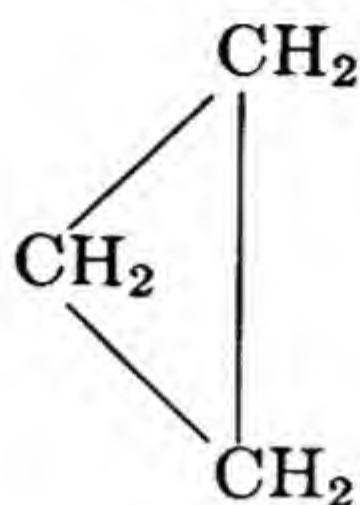


Other reactions of paraffins are considered in the discussion of petroleum at the end of the chapter.

## ► CYCLOPARAFFINS

The paraffin hydrocarbons considered in the preceding section contain carbon *chains*. The members of a closely related type contain carbon *cycles* (or carbon *rings*), hence are called cycloparaffins. Cyclopropane has three carbon atoms arranged in a ring and thus has

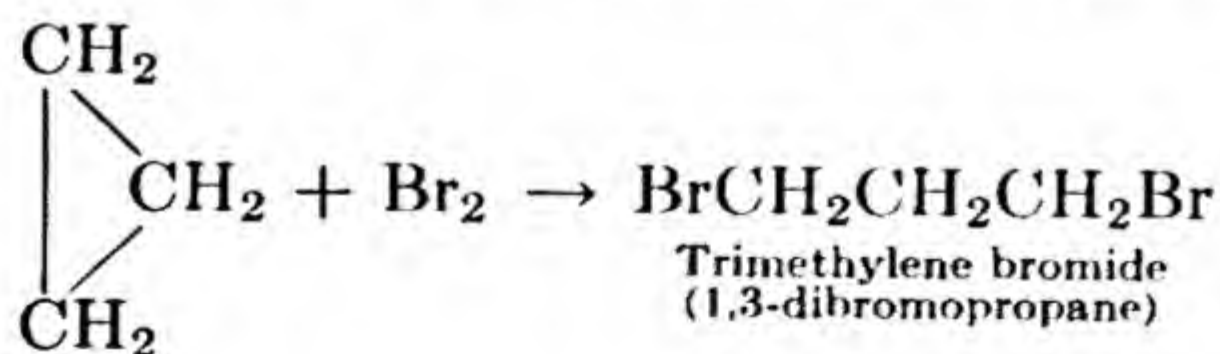
the formula



Cyclobutane, cyclopentane, and cyclohexane are written in a similar fashion. It is to be noted that these compounds contain two less hydrogen atoms than the paraffin of the same number of carbon atoms. They are represented by the general formula  $C_nH_{2n}$ .

		Boiling Point
Cyclopropane		$-34.4^{\circ}$
Cyclobutane		13.0
Cyclopentane		49.5
Cyclohexane		81.4

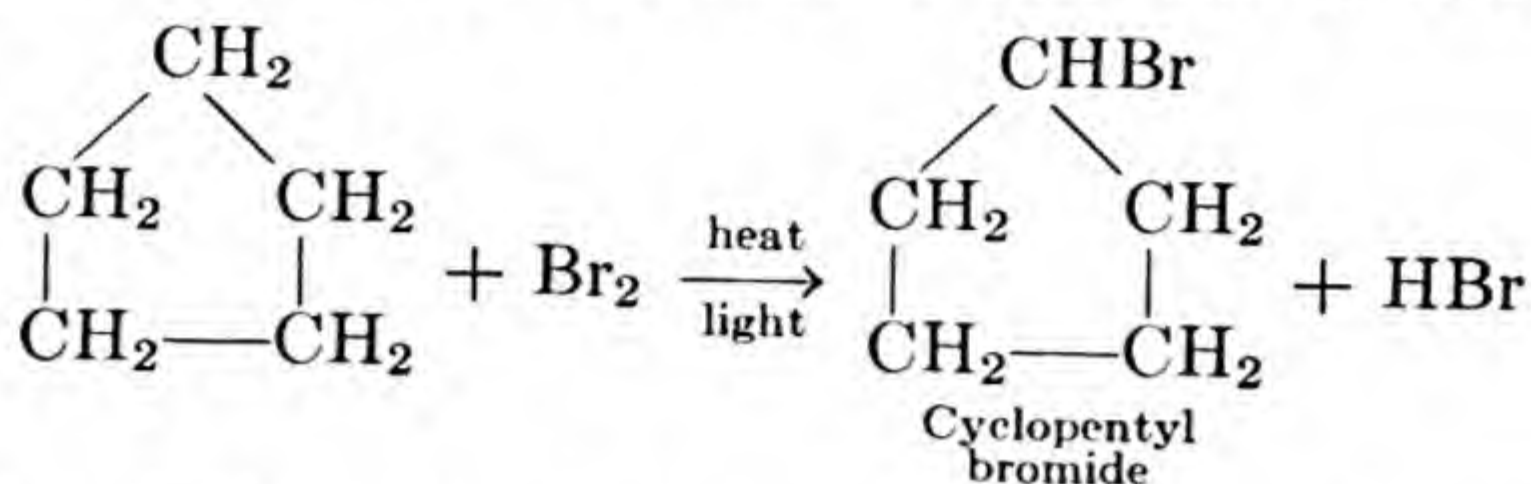
Cyclopropane is much more reactive than its open-chain analog, propane. For example, it reacts with bromine at room temperature and in the absence of light. The product is the open-chain dibromide.



Cyclobutane is less reactive than cyclopropane toward bromine; and cyclopentane and cyclohexane resemble the straight-chain paraf-

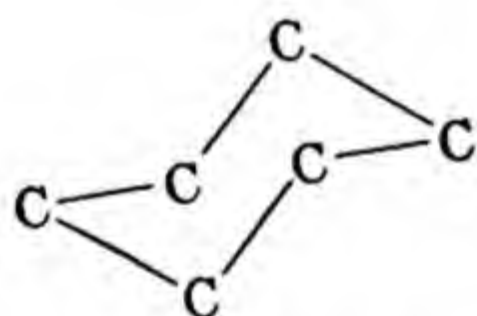


fins. They react with bromine only at elevated temperatures or in the presence of light. The reaction is then one of substitution.



It is believed that the abnormal behavior of cyclopropane is a consequence of the distortion of the carbon valences in the small ring. The angle between any two valence bonds of a tetrahedral atom is about  $109^\circ$ . In order to form a three-membered ring, the angles between the bonds involved must be reduced to  $60^\circ$ . The compression of the valence angles imposes a *strain* upon the molecule, and this strain is supposed to account for the increased reactivity. Cyclobutane would be expected to have less strain, and cyclopentane almost none. Models of cyclohexane and the higher cycloparaffins can be constructed with little or no distortion of the tetrahedral angles. It has been possible to synthesize cycloparaffins which have very large rings—the largest has more than thirty members—the chemical properties of which have been found to resemble those of the paraffins.

Cyclopropane is important commercially as a general anesthetic. Cyclohexane is an airplane fuel and a chemical raw material.



*Arrangement of the Carbon Skeleton in Cyclohexane*

A coplanar arrangement of the carbon atoms comprising rings of six or more members introduces a strain resulting in the distortion of the normal valence angles. Such rings, therefore, ordinarily exist in a non-coplanar structure which is strainless.

## ► PETROLEUM

The origin of petroleum is obscure, but scientists are agreed that it is derived from plant and animal matter which has undergone decomposition over a long period of time. Crude petroleum is primarily a mixture of paraffins and cycloparaffins. The number and complexity of these compounds in petroleum are so great that the analyst has not identified all the components. Moreover, since these com-



pounds have very similar chemical properties, the only method of separating them is by fractional distillation. By this process petroleum is separated into naphtha (ligroin or petroleum ether), gasoline, kerosene, diesel fuel, lubricating oils, and paraffin wax—to mention a few of the more useful fractions. Each of these is still a mixture of a large number of individual compounds. The chart gives some idea of the separation and approximate composition of these various materials.

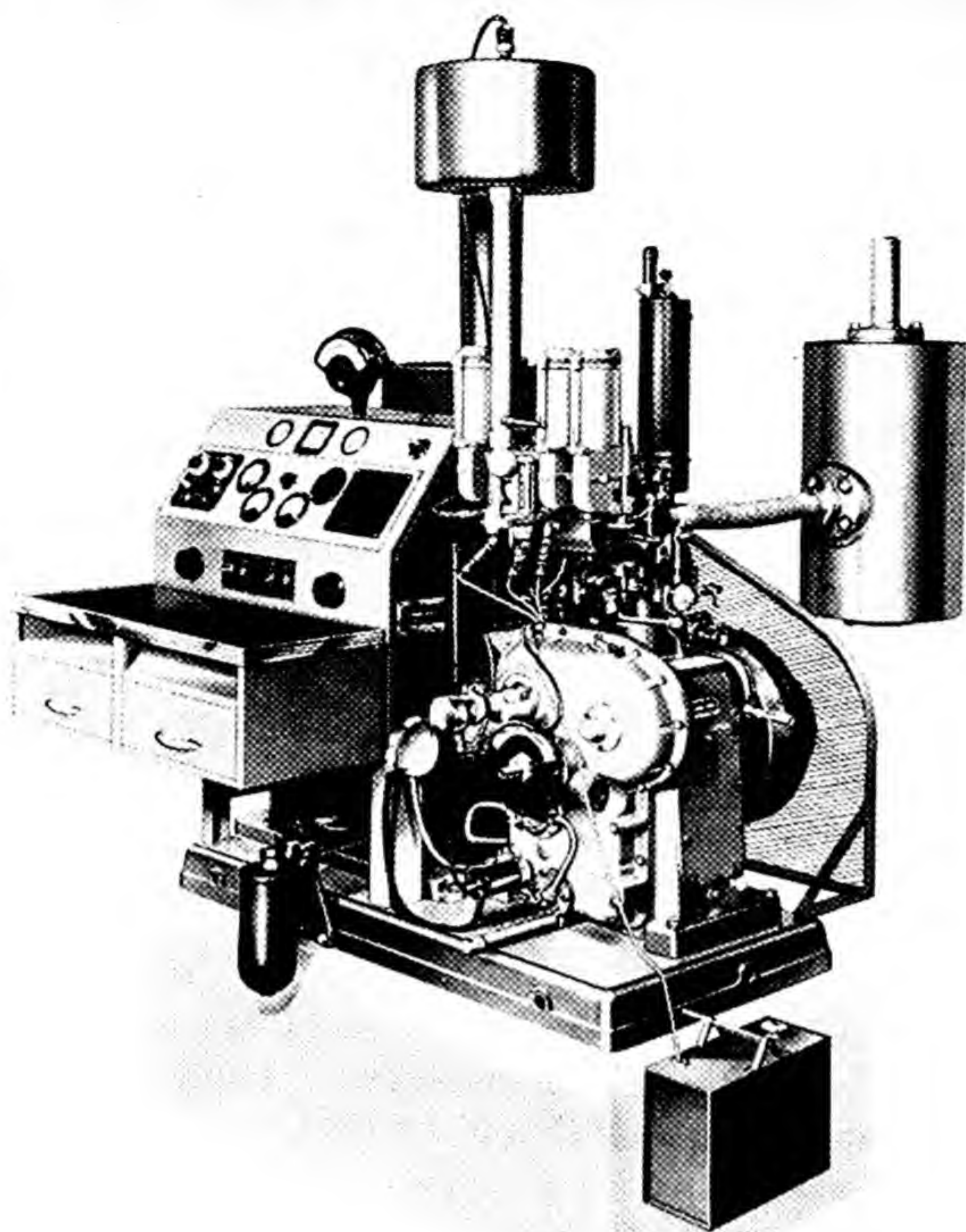
### Products from Fractional Distillation of Petroleum

Boiling Point	Composition	Name
Gaseous	$\text{CH}_4\text{—C}_4\text{H}_{10}$	Natural gas
–40 to –5°	$\text{C}_3\text{H}_8\text{—C}_4\text{H}_{10}$	Propane, butane
20 to 100°	$\text{C}_5\text{—C}_7$	Ligroin, petroleum ether
30 to 210°	$\text{C}_5\text{—C}_{12}$	Gasoline
150 to 205°	$\text{C}_8\text{—C}_{12}$	Cleaner's naphtha
150 to 260°	$\text{C}_8\text{—C}_{14}$	Kerosene
175 to 340°	$\text{C}_{10}\text{—C}_{20}$	Diesel fuel
	$\text{C}_{16}\text{—C}_{22}$	Mineral oil, lubricating oils
	$\text{C}_{20}\text{—C}_{26}$	Paraffin wax
Residue		Asphalt, petroleum coke

Numerous other useful products from petroleum can be obtained by distillation or other methods. Greases, for example, are made from mixtures of soaps (Chapter 11) and lubricating oils.

The various processes for working up petroleum have been constantly changing. The reasons are the change in consumer demand and the improvement in processing. Kerosene was once the most valuable petroleum product, but the advent of the automobile caused the value of gasoline to increase sharply so that it is now desirable to convert the higher boiling fractions into gasoline. The situation was further complicated by improvements in the gasoline engine, which can be realized only by the use of higher quality gasoline. The gasoline obtained by direct distillation (straight-run gasoline) proved to be a poor fuel. Improvement can be effected by the addition of lead tetraethyl,  $\text{Pb}(\text{CH}_2\text{CH}_3)_4$ , and most present-day gasolines contain some of it. The measurement of the quality of a gasoline is made by comparing its tendency to “knock” with standard fuels, using an arbitrary standard based upon *n*-heptane (a very poor fuel) as zero and 2,2,4-trimethylpentane (an excellent fuel) as 100. Thus a gasoline with an “octane number” of 86 is equivalent to a mixture of 86% 2,2,4-trimethylpentane and 14% *n*-heptane in a test engine.



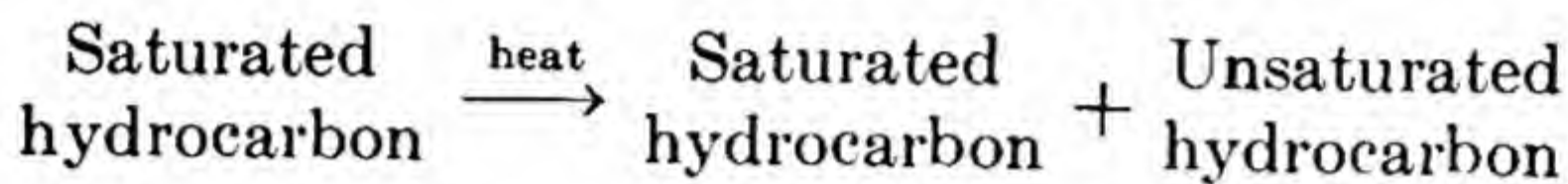
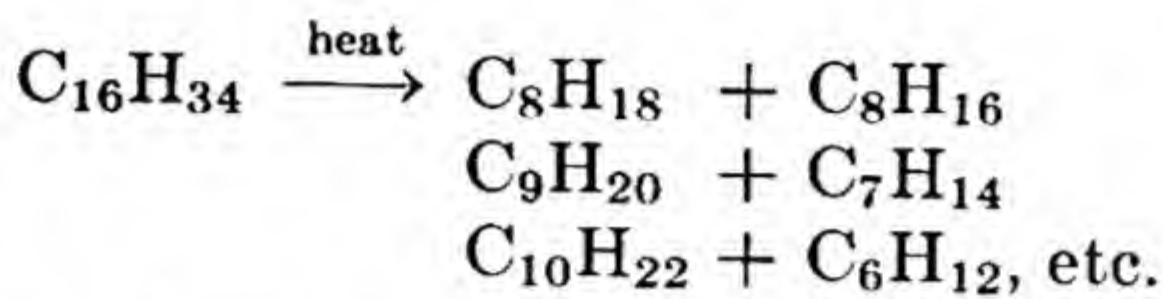


An octane rating unit used to determine the octane number of a gasoline. The amount of knocking produced in the engine by the test gasoline is compared with that produced by standard mixtures. (Photograph furnished by the Waukesha Motor Company.)

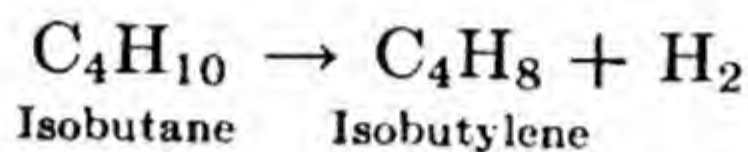
By the distillation of crude petroleum about one gallon of gasoline per five gallons of crude oil is obtained. The yield of gasoline can be doubled by the cracking process and other processes dependent upon it.

Cracking converts fractions of high boiling range in part into lower boiling material useful as gasoline. The process is essentially a thermal or catalytic decomposition in which the carbon chains are

broken. When this occurs only one of the two fragments can form a new saturated hydrocarbon. The second product must contain fewer hydrogen atoms than the corresponding saturated hydrocarbon. The process may be illustrated by a specific compound, such as  $C_{16}H_{34}$ .

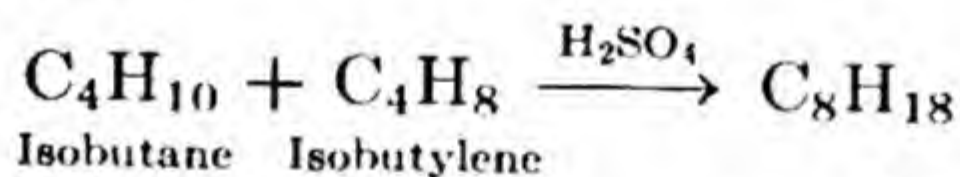
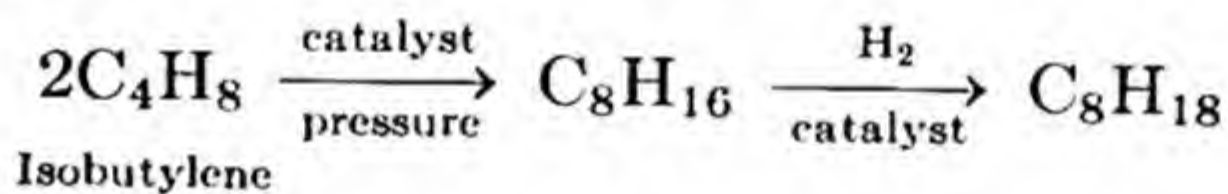


Unsaturated hydrocarbons may also be obtained from paraffins by dehydrogenation. For example, isobutane is converted to isobutylene when it is heated in the presence of a metal oxide catalyst:



Large quantities of isobutylene are manufactured by this process.

The yield and quality of gasoline have been still further improved by the utilization of the gaseous hydrocarbons produced in the cracking process. This development may be illustrated by the reaction of isobutylene with itself or with isobutane.



The diesel engine has attained considerable prominence since World War II, and the petroleum industry has had to adjust itself to take care of the new demand. For gasoline engines it has been found that the best fuels contain hydrocarbons with branched chains, whereas the best diesel fuels have straight-chain hydrocarbons. Therefore, the rise of the diesel engine might have been expected to cause considerable dislocation in the petroleum industry, but the problem has been solved by the industry with no discomfort to its customers.

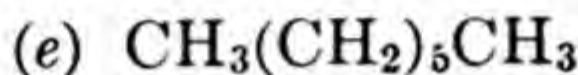
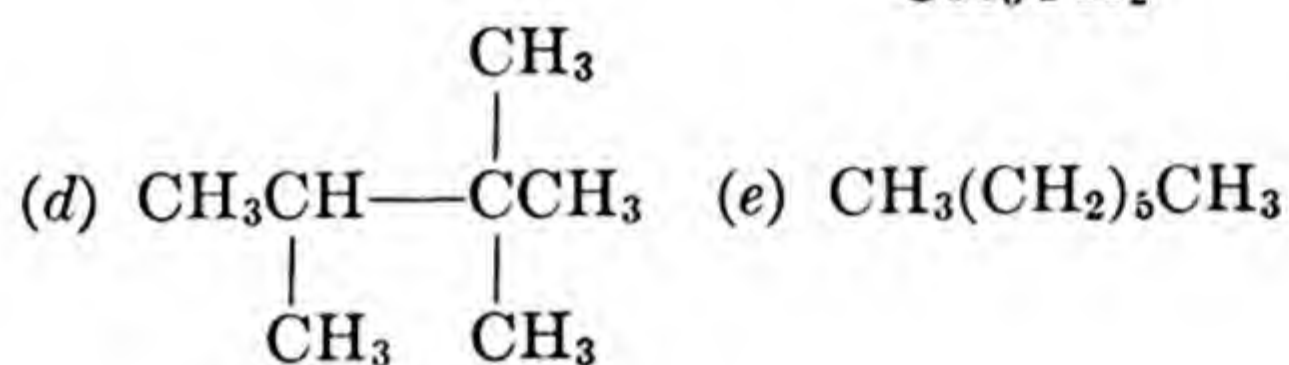
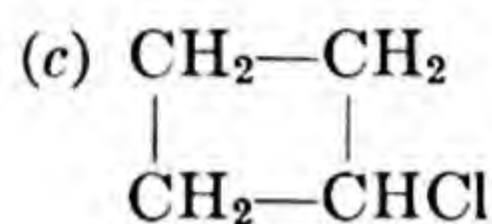
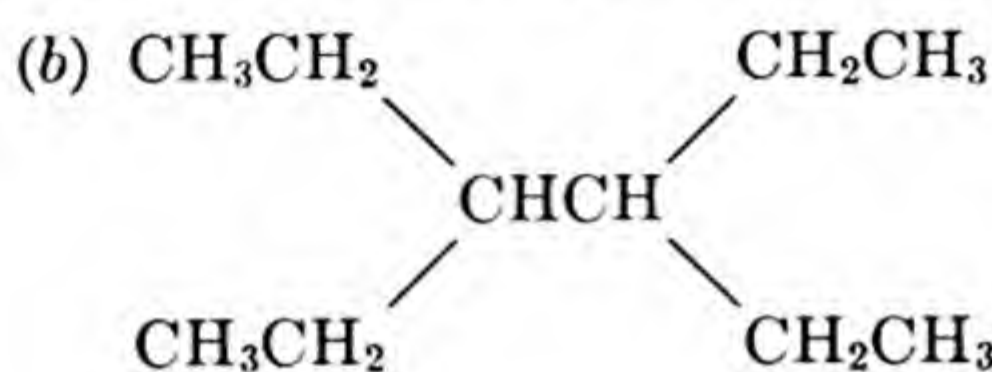
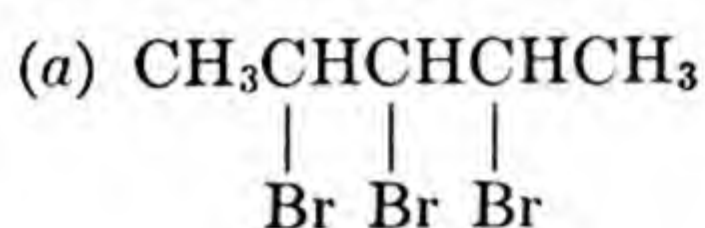


▶ **QUESTIONS** \_\_\_\_\_

1. Show by a chart all the products which can be obtained by the chlorination of propane.

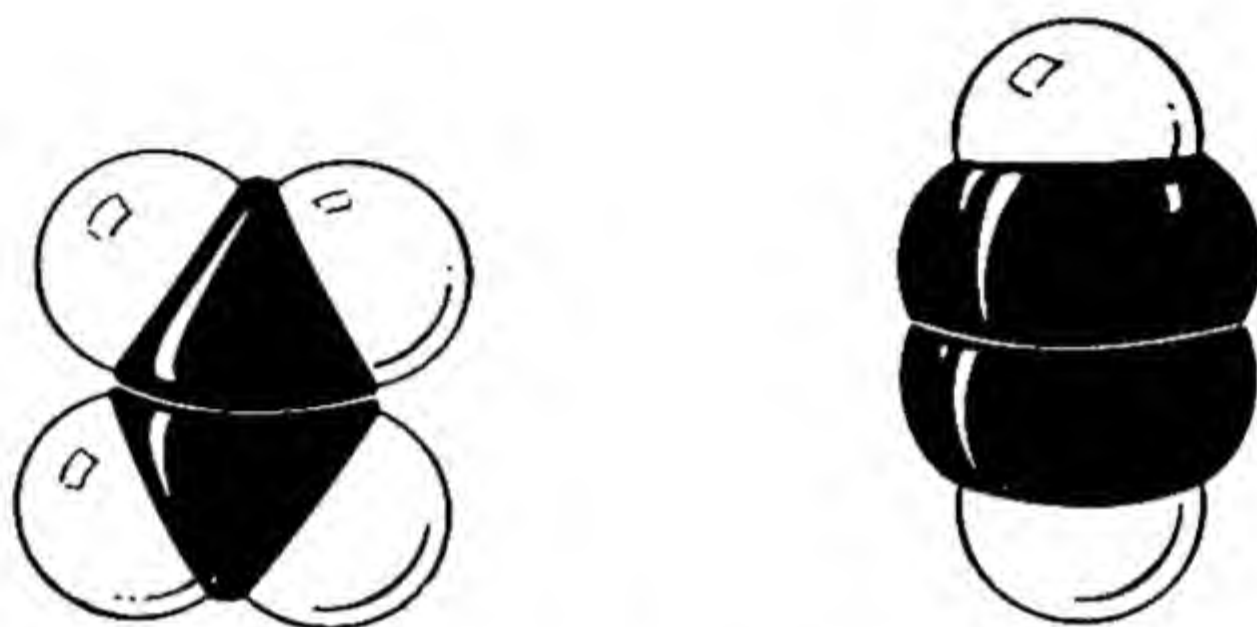
2. Write structural formulas for the following compounds: 2,2,3-trimethylpentane; 1,3-dibromocyclopentane; 3-ethyl-4-methylhexane, 2-bromo-2-chlorobutane.

3. Give systematic names for the following structures:





# *Unsaturated hydrocarbons*



The simplest types of unsaturated hydrocarbons are the olefins and the acetylenes. In ethylene,  $\text{CH}_2=\text{CH}_2$ , the first member of the olefin series, the carbon atoms are linked by two pairs of electrons, and the molecule is essentially planar. In acetylene,  $\text{HC}\equiv\text{CH}$ , the carbon atoms are linked by three pairs of electrons, and the molecule is linear.

## ► OLEFINS (ALKENES)

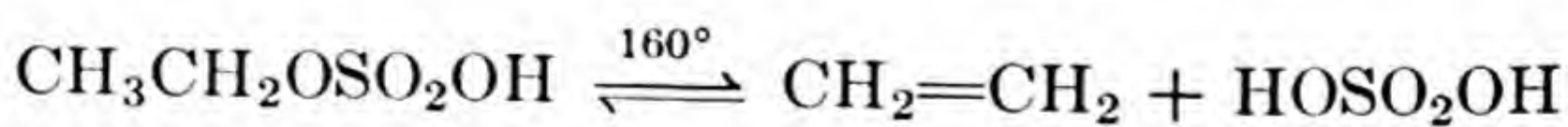
Open-chain hydrocarbons having fewer hydrogen atoms than the corresponding paraffins are said to be unsaturated. Those whose composition conforms to the general formula  $\text{C}_n\text{H}_{2n}$  are known as olefins or alkenes. The names of the lower members of the series are derived from those of the corresponding saturated hydrocarbons by changing the ending "ane" to "ylene." As can be seen from the structural formulas of these substances, their distinguishing feature, or functional group, is the union of two carbon atoms by a double bond. For this type of link, a suffix -ene is used in systematic nomenclature. Since the double bond may occur in various places in the chain, it is often necessary to employ locating numbers, as in

1-butene and 2-butene. The number used is the smaller of the two designating the carbon atoms involved in the double bond.

Olefins		
Name	Formula	Boiling Point
Ethylene	$\text{CH}_2=\text{CH}_2$	$-104^\circ$
Propylene	$\text{CH}_3\text{CH}=\text{CH}_2$	$-47$
1-Butene	$\text{CH}_3\text{CH}_2\text{CH}=\text{CH}_2$	$-5$
2-Butene	$\text{CH}_3\text{CH}=\text{CHCH}_3$	$2$
Isobutylene	$\text{CH}_3\text{C}=\text{CH}_2$	$-6$
	$\begin{array}{c}   \\ \text{CH}_3 \end{array}$	
1-Pentene	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$	$30$
2-Pentene	$\text{CH}_3\text{CH}_2\text{CH}=\text{CHCH}_3$	$36$
2-Methyl-2-butene	$\text{CH}_3\text{C}=\text{CHCH}_3$	$38$
	$\begin{array}{c}   \\ \text{CH}_3 \end{array}$	
3-Methyl-1-butene	$\text{CH}_3\text{CHCH}=\text{CH}_2$	$25$
	$\begin{array}{c}   \\ \text{CH}_3 \end{array}$	
2-Methyl-1-butene	$\text{CH}_3\text{CH}_2\text{C}=\text{CH}_2$	$31$
	$\begin{array}{c}   \\ \text{CH}_3 \end{array}$	

**Ethylene.** The first member of the olefin series is ethylene,  $\text{CH}_2=\text{CH}_2$ . It is obtained commercially in large amounts in the cracking process, along with propylene, isobutylene, and higher olefins. Ethylene is a colorless gas, with a sweet odor, which produces unconsciousness when inhaled. Another interesting property is its ability to influence the color of certain fruits. Oranges, lemons, grapefruit, tomatoes, and other fruits assume a deeper color when exposed to ethylene. In this sense, ethylene is useful as a "ripeners," particularly of citrus fruits. Since ethylene has become available in large quantities, it has been employed to manufacture many useful and interesting compounds, among which are ethyl alcohol, ethyl ether, ethylene glycol, and mustard gas.

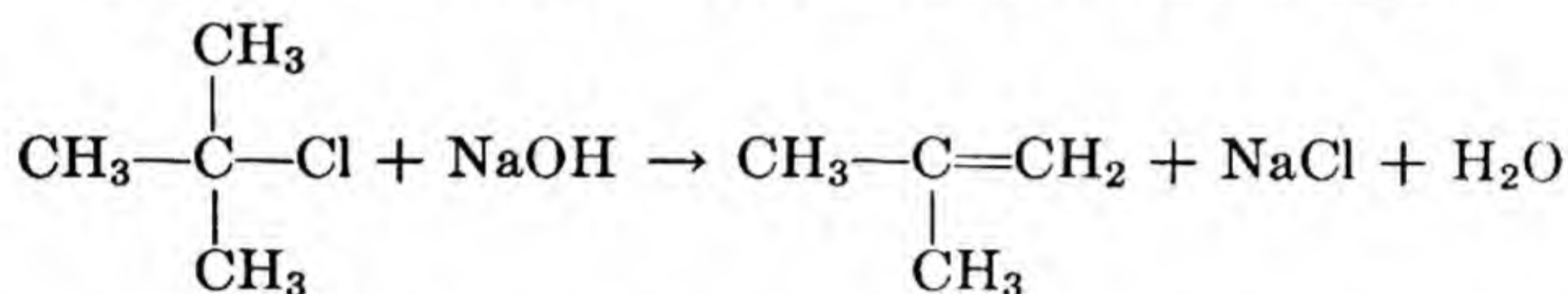
Ethylene is usually prepared in the laboratory by treating alcohol with sulfuric acid. The first step in the process is the formation of ethylsulfuric acid—a reaction which is reversible. This compound is unstable to heat and decomposes to give ethylene and sulfuric acid. The second step can be reversed by operating at lower temperatures.





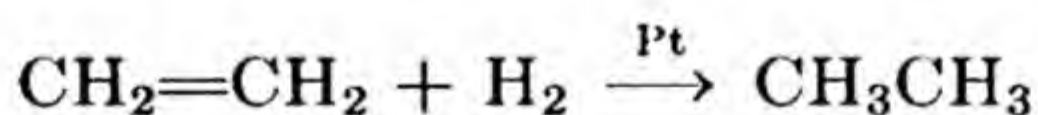
Because it is regenerated in the process sulfuric acid is to be regarded as a catalyst. Phosphoric acid, aluminum oxide, and clay are useful catalysts also, and have been employed for the commercial preparation of ethylene from alcohol. The low cost of ethylene from cracking, however, has made the reverse process—the manufacture of alcohol from ethylene—an economical one.

Olefins can be obtained also from the alkyl halides by dehydrohalogenation, a process which consists in the removal of halogen acid through the agency of alcoholic sodium or potassium hydroxide.

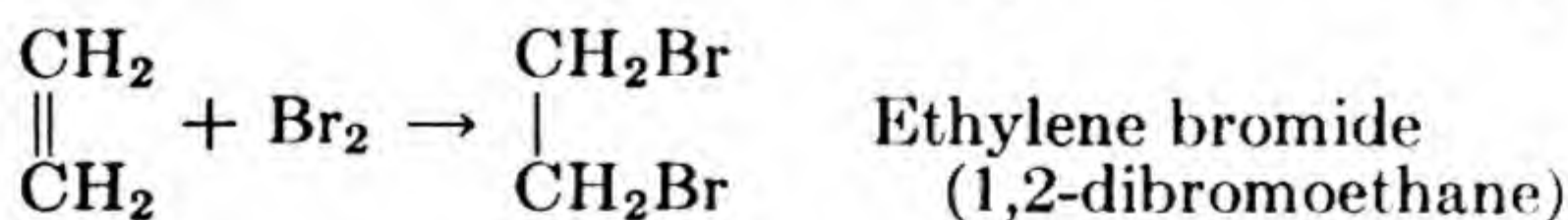
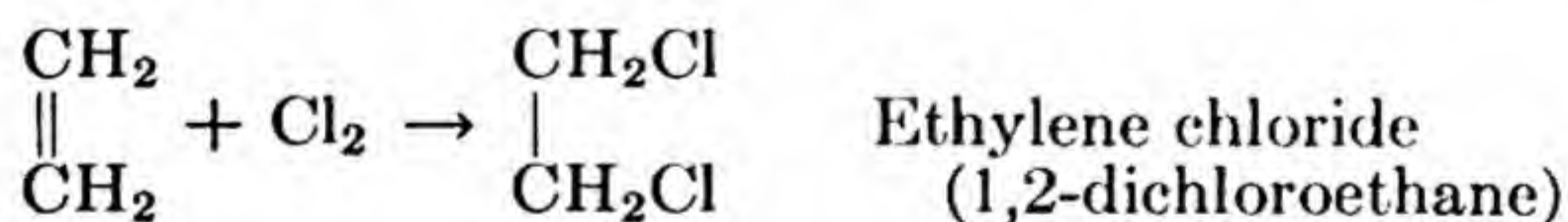


**Reactions of ethylene.** Two carbon atoms joined by a double bond ( $-\text{C}=\text{C}-$ ) may be looked upon as the functional group of the olefins because this group is responsible for the reactions that characterize the class. These reactions are all of the type known as *addition* reactions, and they evidently owe their driving force to the tendency of unsaturated compounds to become saturated. Addition reactions always involve the combination of two or more molecules to give a single product.

Ethylene reacts with a wide variety of reagents and almost always in such a manner as to lead to the formation of a saturated derivative. Thus hydrogen in the presence of a catalyst such as platinum yields ethane.

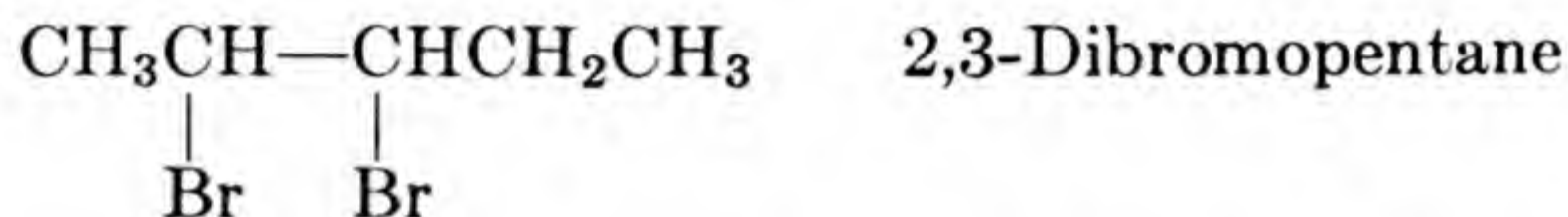
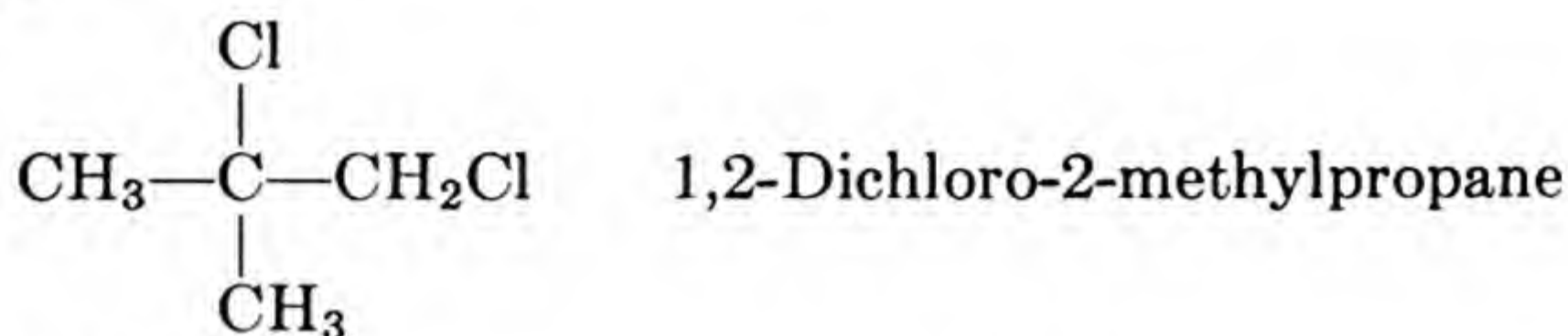
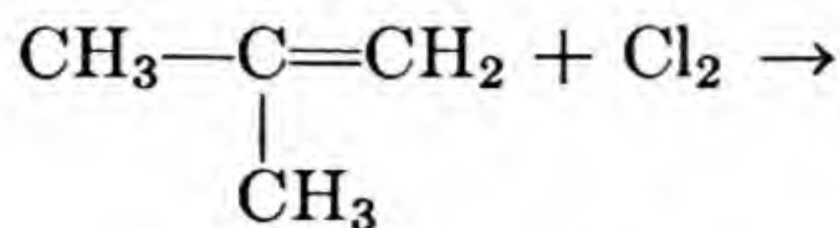
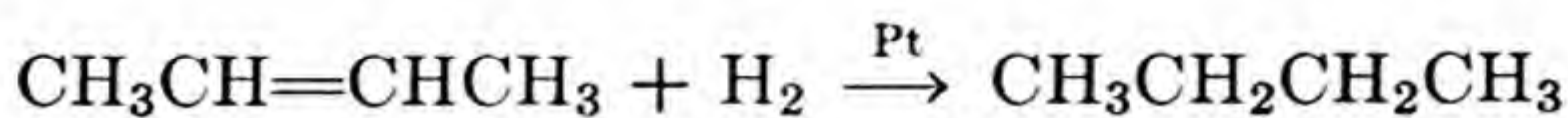


Chlorine and bromine add readily to the double bond to produce the corresponding ethylene halides.



These reactions are not specific for ethylene but are general for all compounds having normal carbon-carbon double bonds.





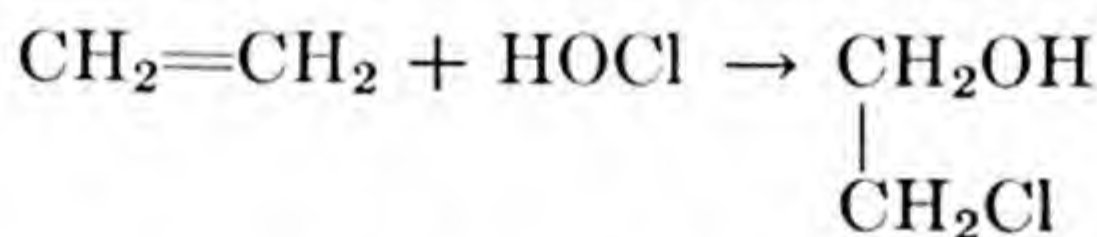
We have noted that sulfuric acid converts ethylene into ethylsulfuric acid. Other acids react similarly.



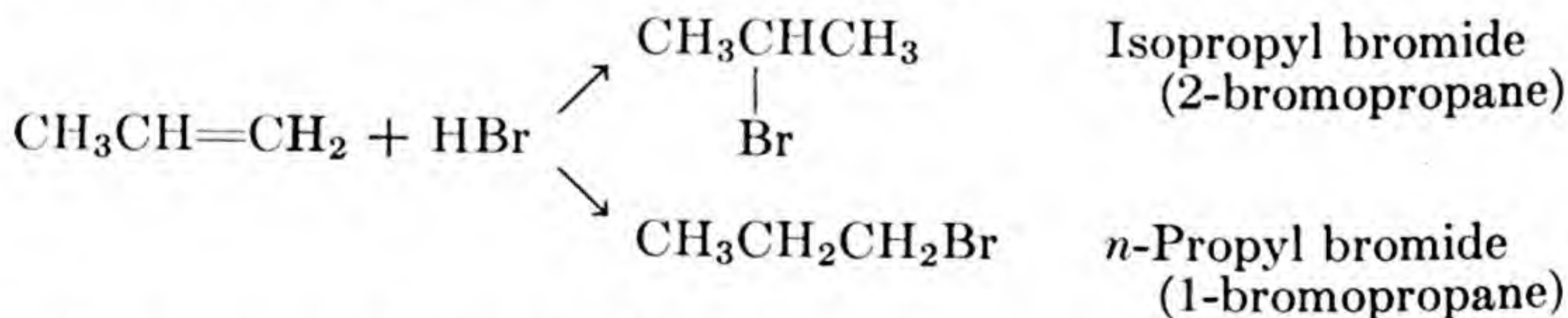
The addition of hydrogen bromide, for example, leads to the formation of ethyl bromide.



Hypochlorous acid (HOCl) gives ethylene chlorohydrin, a compound which has the unusual property of hastening the germination of new potatoes. It is readily converted into many useful products.

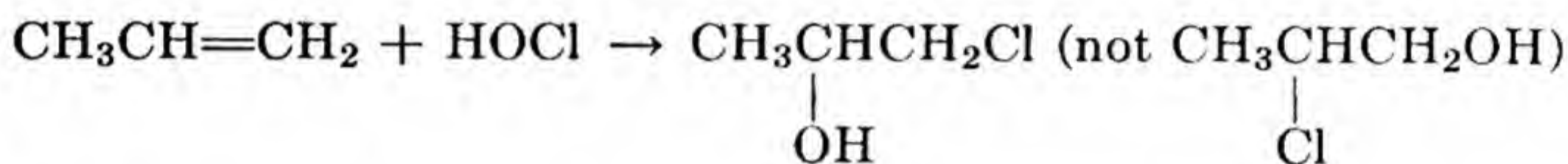
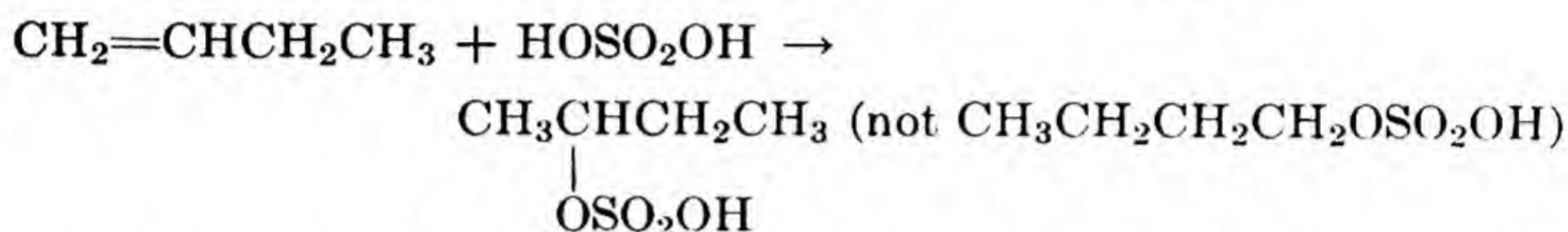
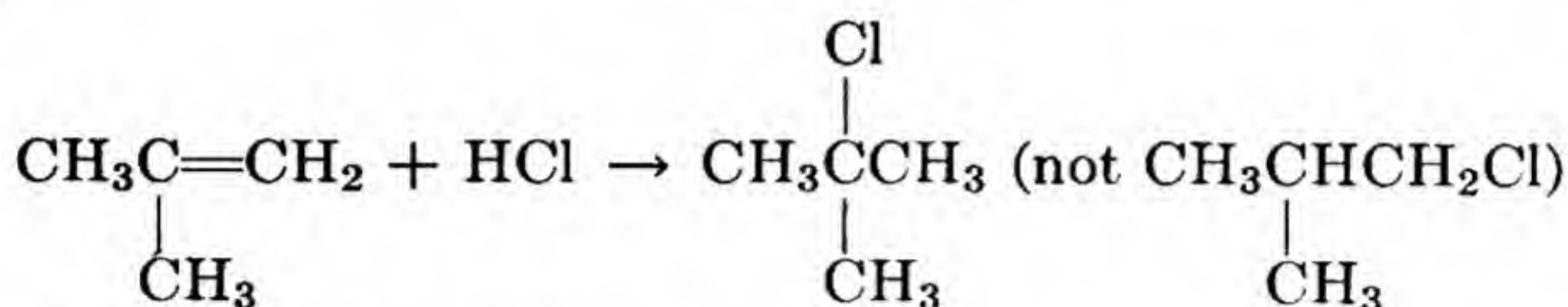


Reagents such as sulfuric acid, the hydrogen halides, and hypochlorous acid are said to be unsymmetrical; that is, the two portions which add to the carbon atoms of the double bond are different. When such a reagent reacts with an unsymmetrical unsaturated hydrocarbon two products appear to be possible:

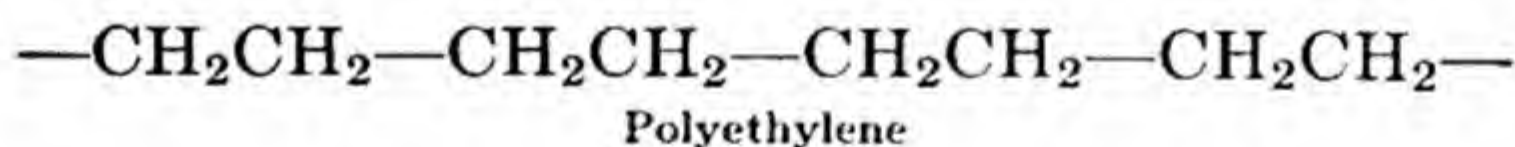


In this example isopropyl bromide is the sole product except under special conditions. Examination of a large number of similar examples has led to the generalization, known as *Markovnikoff's*

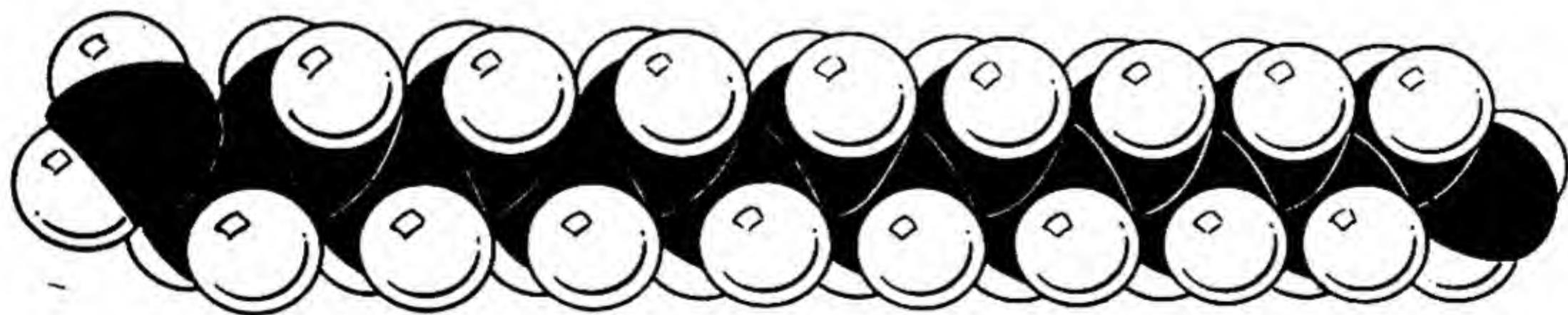
*rule: When an unsymmetrical reagent adds to an unsymmetrical unsaturated hydrocarbon, the positive part of the reagent becomes attached to the carbon having more hydrogen atoms. In most cases the hydrogen of the reagent is the positive part; with hypochlorous acid, it is chlorine. Further examples of the application of the rule follow:*



When ethylene is treated under high pressure with certain catalysts, such as peroxides, it undergoes reaction with itself. The product is a white, waxy solid called polyethylene which has excellent plastic and electrical insulating properties. It is composed of a large number of ethylene residues linked to form a long chain.



Such a substance, having a high molecular weight and a continuously repeating structural feature, is said to be a *polymer*. The substance from which it is made (in this case, ethylene) is said to be a *monomer*.



The model shows a segment of the polyethylene chain, containing nine  $\text{—CH}_2\text{CH}_2\text{—}$  groups.

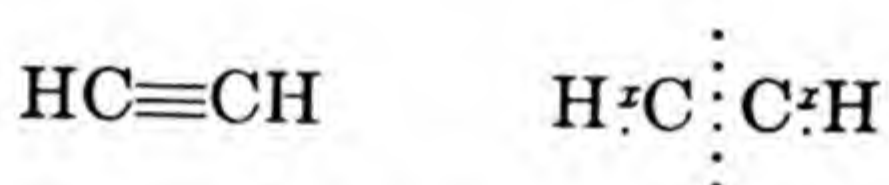


Several processes have been developed for the commercial polymerization of ethylene. By the use of appropriate catalysts, polymerization can be effected under a wide variety of conditions of temperature and pressure, and the properties of the product can be varied over fairly wide ranges. Some of the processes are adaptable to the polymerization of other olefins, especially propylene. The production of polyethylene has increased tremendously because of its impressive properties. The polymer is innately flexible so that no plasticizer is needed; it is readily molded; it has excellent electrical insulating properties; and the raw material is cheap.

Polymers occur in nature (proteins, starch, rubber), and many polymers synthesized commercially (Bakelite, nylon, Vinylite) are valuable materials.

### ► ACETYLENES

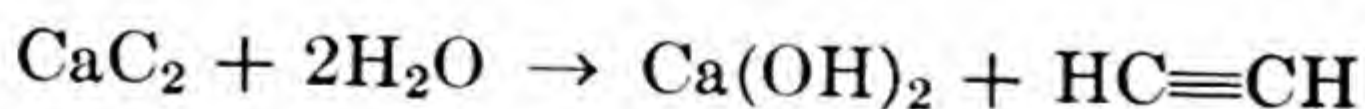
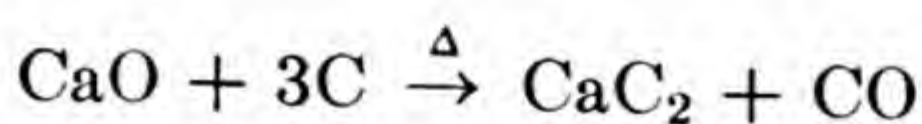
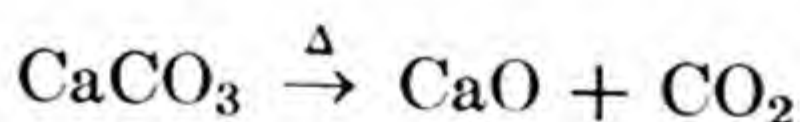
The acetylenes are hydrocarbons having a triple bond (six shared electrons); their general formula is  $C_nH_{2n-2}$ . The first member of the series is acetylene, and it is the only homolog of commercial significance. It is a colorless gas which burns with oxygen to give



Acetylene

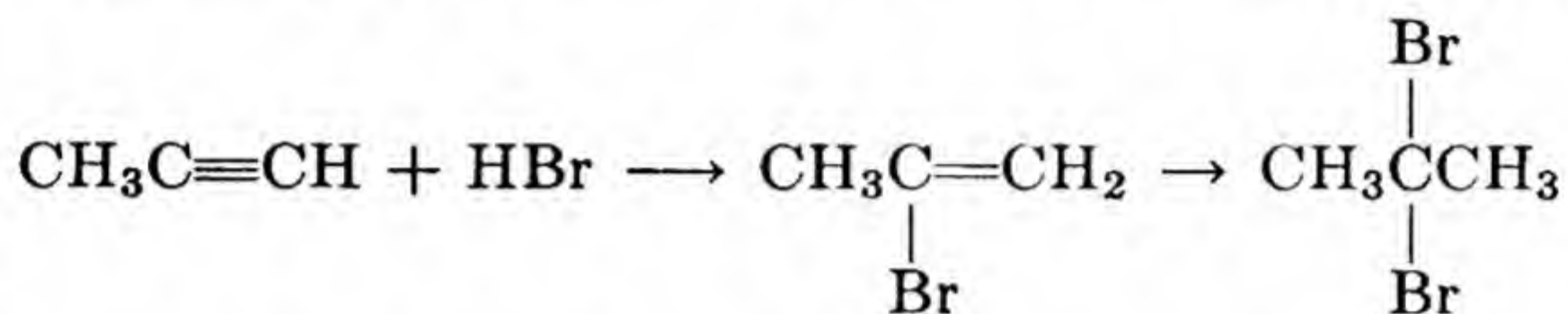
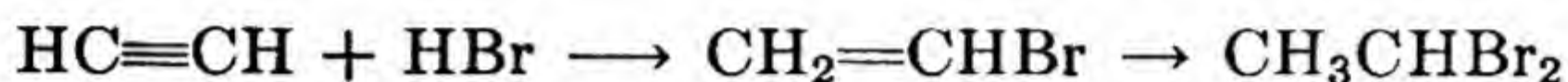
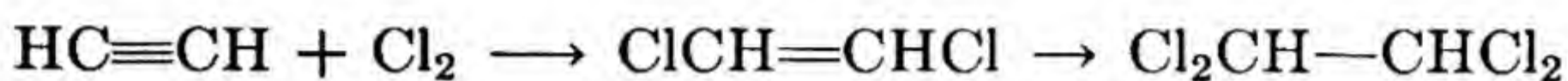
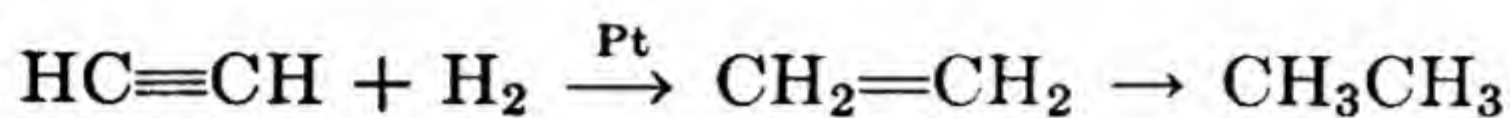
a very hot luminous flame; for this reason it finds use in cutting and welding torches. Since it is dangerously explosive under pressure, acetylene is stored in cylinders containing acetone and pumice; under these conditions it is stable. Large quantities of acetylene are used industrially in the manufacture of acetic acid and acetic anhydride, which are important industrial chemicals, and in the manufacture of neoprene (see p. 37).

Acetylene is made by the partial combustion of methane or by the hydrolysis of calcium carbide, for which the raw materials are coke and limestone.

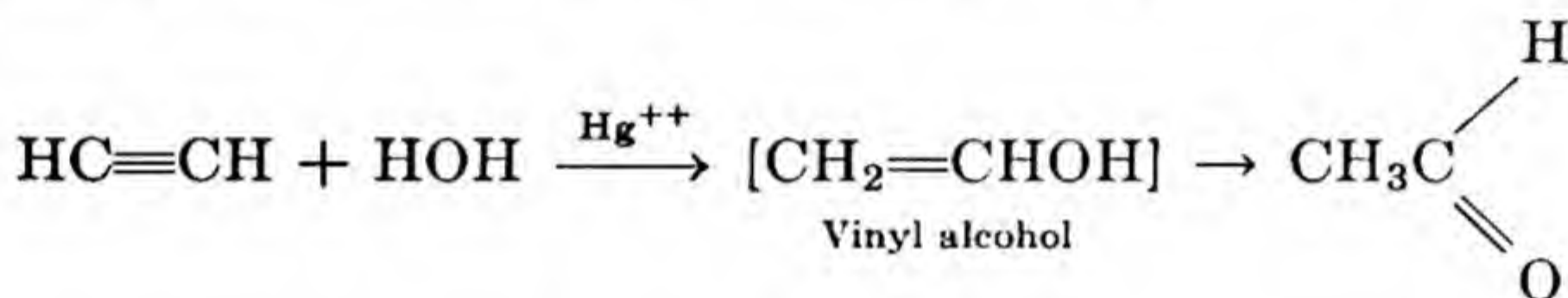




The reactions of acetylene and its homologs are chiefly of the addition type, and thus they resemble those of the olefins. Being more unsaturated, however, they are capable of adding two molecules of reagent.

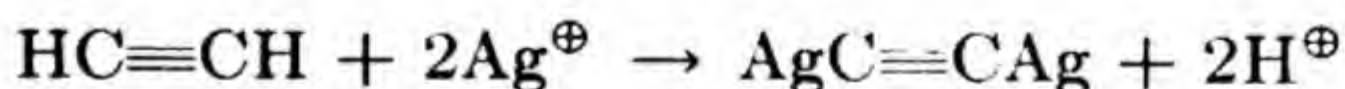
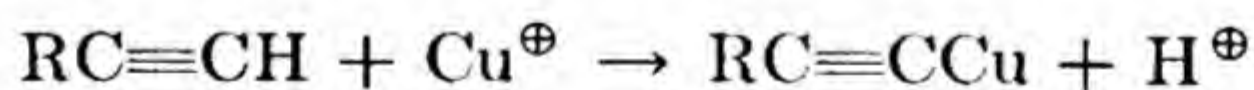
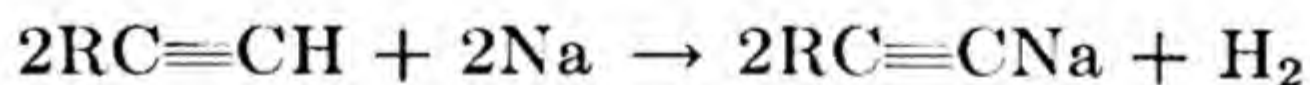


The acetylenes will add water under special conditions. Mercuric salts catalyze the reaction. The brackets surrounding the formula



for vinyl alcohol indicate that it is unstable.

Acetylenes which contain the linkage  $-\text{C}\equiv\text{CH}$  are said to be terminal acetylenes: they have very weakly acidic properties. The terminal hydrogen atom in such compounds can be replaced by active metals, such as sodium or potassium, or by cuprous or silver ions in ammoniacal solution. Acetylene, since it has two terminal hydrogen atoms, forms a disubstituted derivative. Other terminal acetylenes form monosubstituted compounds. The cuprous and silver



acetylides are insoluble in water and are dangerously explosive when dry. The fact that acetylenes of the type  $\text{RC}\equiv\text{CR}'$  do not give a precipitate with ammoniacal cuprous or silver salts can be used to distinguish them from terminal acetylenes.

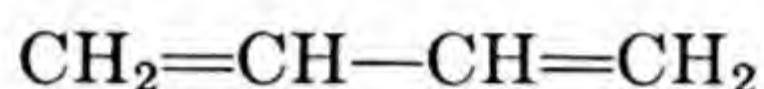
Acetylene is the raw material for a great number of industrial chemicals. Among the more important may be mentioned chloroprene, vinyl chloride, vinyl acetate, acrylonitrile, acetaldehyde, acetic



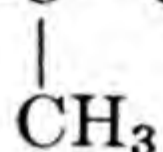
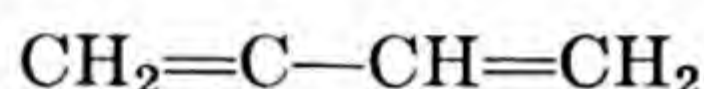
anhydride, acetic acid, trichloroethylene, and tetrachloroethylene. The preparations of these compounds from acetylene are noted in the appropriate chapters.

## ► DIOLEFINS

Hydrocarbons having two double bonds are said to be diolefins, or dienes. They have the same general formula,  $C_nH_{2n-2}$ , as the acetylenes. The most important are 1,3-butadiene and isoprene. Both of these hydrocarbons have alternate double and single bonds in their

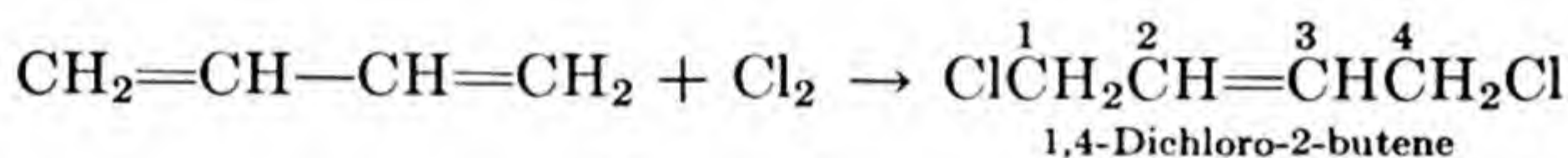


1,3-Butadiene

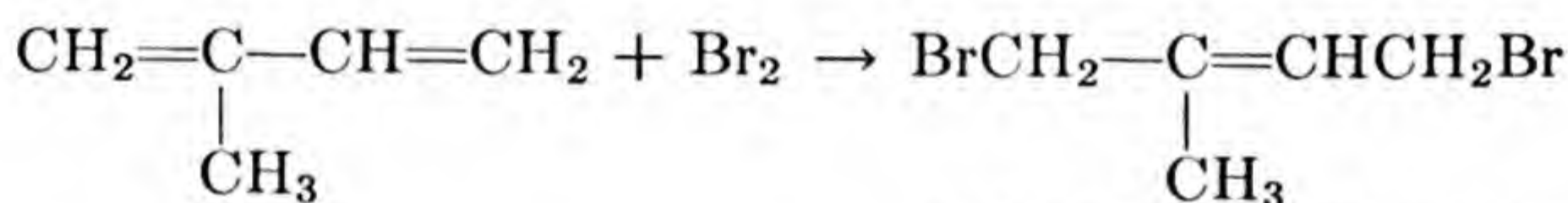


Isoprene

chains. Such arrangements are described as *conjugated* systems. They are peculiar in that addition can occur at the ends of the system. When *conjugate addition* takes place, a shift of electrons is necessary

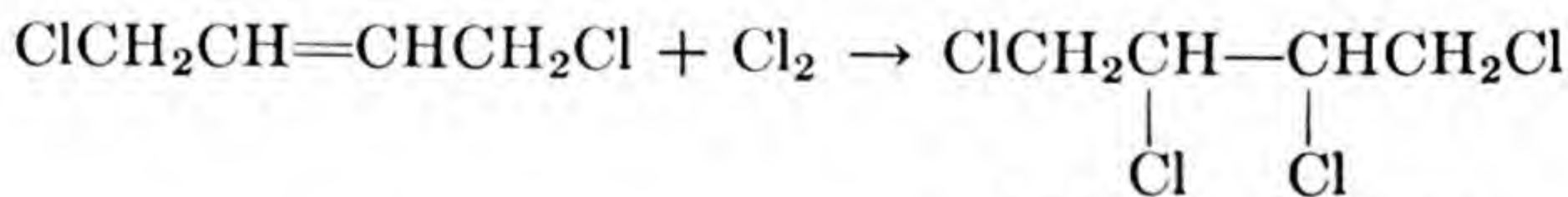


1,4-Dichloro-2-butene



1,4-Dibromo-2-methyl-2-butene

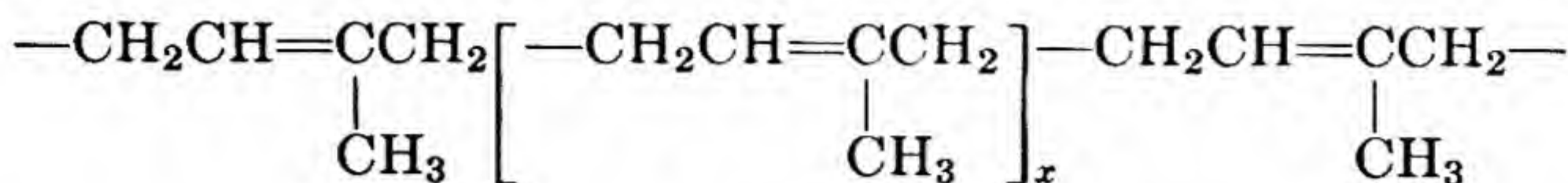
in order to satisfy the valence demands of the atoms involved, so that a double bond appears in the 2,3-position. The new double bond can undergo the usual addition reactions, so that the final product may be saturated.



1,2,3,4-Tetrachlorobutane

Butadiene can be obtained from butane or from higher petroleum fractions. Isoprene is formed by the dehydrogenation of isopentane and by the destructive distillation of rubber. When it is treated with sodium, isoprene combines with itself to produce a polymer which resembles natural rubber. It is believed that isoprene reacts with itself by conjugate addition to form this product, and in natural

rubber isoprene units are similarly joined. The number of isoprene



Rubber

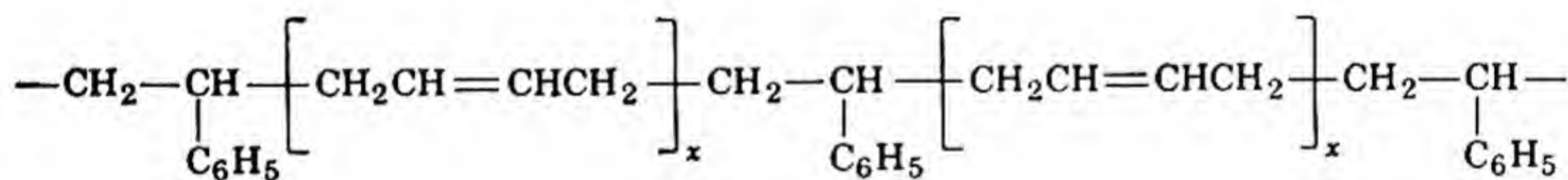
units ( $x$  in the formula) appears to be about 10,000 in natural rubber.

## ► SYNTHETIC RUBBERS

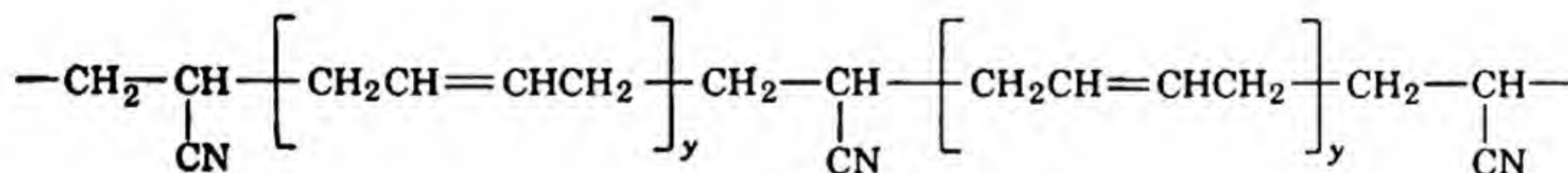
The term “synthetic rubber” has been inaccurately used because most of these products are different in composition from natural rubber, though their physical properties are similar. A superior term is *elastomer*. When butadiene is treated with sodium a polymer with rubberlike properties results. The product was used as a sub-



stitute for rubber in Germany during World War I, but it has been supplanted by newer products. Improvement has been most successfully accomplished by the simultaneous polymerization (copolymerization) of butadiene with other substances, such as styrene,  $\text{C}_6\text{H}_5\text{CH}=\text{CH}_2$ , or acrylonitrile,  $\text{CH}_2=\text{CHCN}$ , under the influence of catalysts other than sodium. The products GR-S and GR-N are similar to natural rubber and, like it, can be vulcanized.

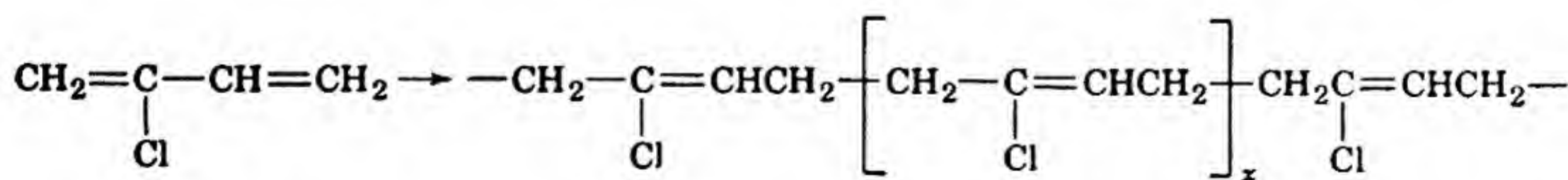


GR-S (simplified)



GR-N (simplified)

A synthetic rubber similar in structure to those just mentioned is neoprene, which is made from chloroprene (2-chloro-1,3-butadiene).

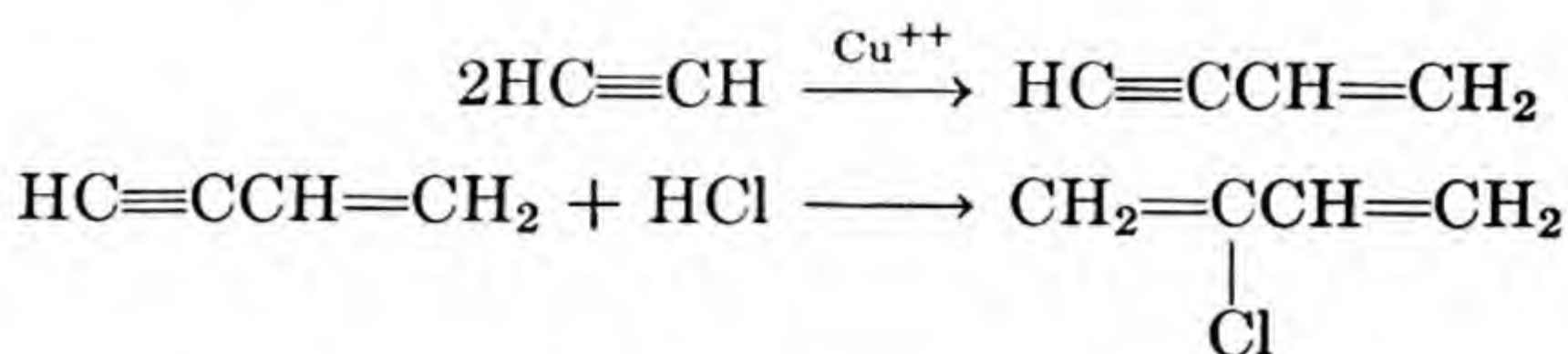


Chloroprene

Neoprene

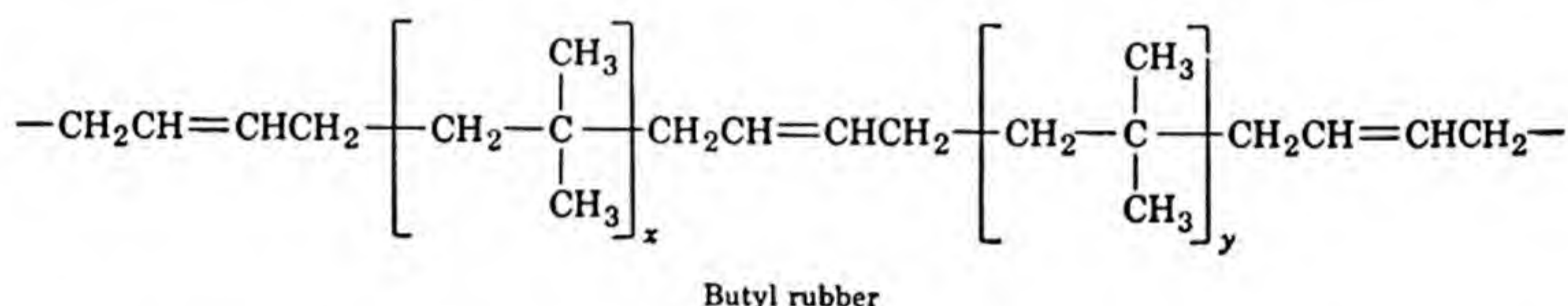


Chloroprene is prepared from acetylene, as shown by these equations:



Neoprene is widely used in gasoline hoses and gaskets which come in contact with organic liquids. Natural rubber and most of the synthetic rubbers become sticky, swell badly, and lose their strength in contact with organic solvents. Neoprene is much less affected.

Another rubberlike material manufactured in large amounts is butyl rubber, which is obtained by the polymerization of isobutylene

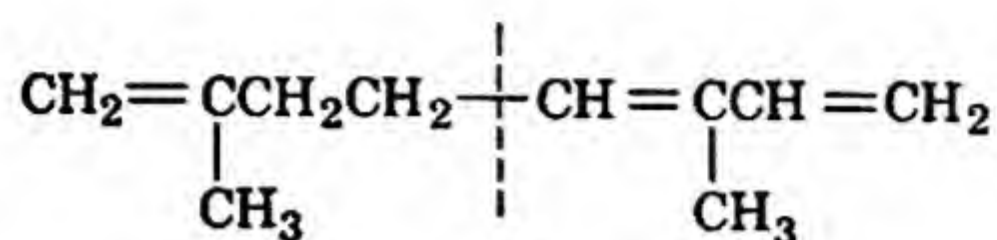


with a small percentage of isoprene or butadiene. It is especially useful in the inner tubes of pneumatic tires, for it is comparatively impervious to the passage of gases.

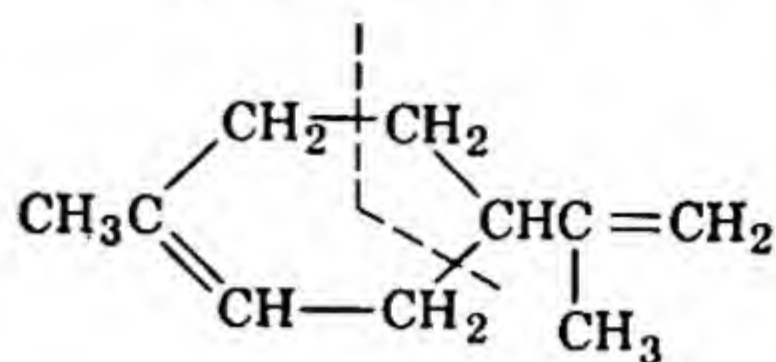
## ► TERPENES

A great number of compounds which have the molecular formula  $\text{C}_5\text{H}_8$ , or some integral multiple thereof, or which can be considered as derivatives of such hydrocarbons, occur in nature. These compounds comprise alcohols, aldehydes, ketones, and acids, as well as hydrocarbons, and are called *terpenes*. A remarkable feature of the terpenes is that their carbon skeletons are arranged in such a way that they may be considered as composed of isoprene units. This generality is known as the isoprene rule. In the structural formulas in this section the isoprene units are set off by broken lines.

Terpene hydrocarbons are called monoterpenes if their molecular formula is  $\text{C}_{10}\text{H}_{16}$ , sesquiterpenes if it is  $\text{C}_{15}\text{H}_{24}$ , and diterpenes if it is  $\text{C}_{20}\text{H}_{32}$ , etc. Terpenes may or may not possess rings. Ocimene, which is found in the leaves of various plants, is an acyclic monoterpene. Cyclic monoterpenes have six-membered rings. Limonene,

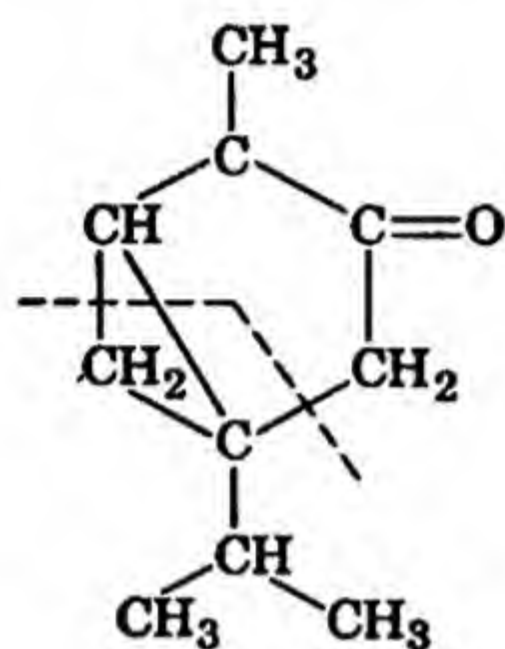


Ocimene

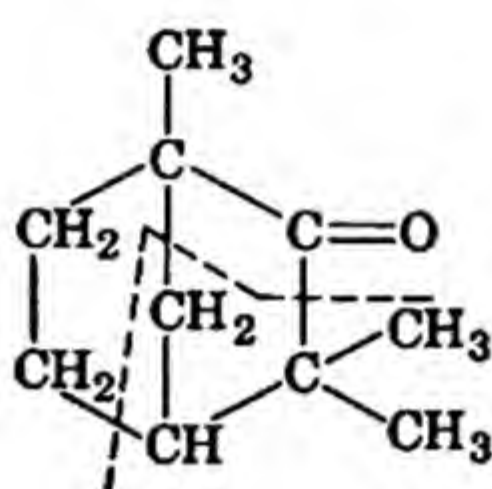


Limonene

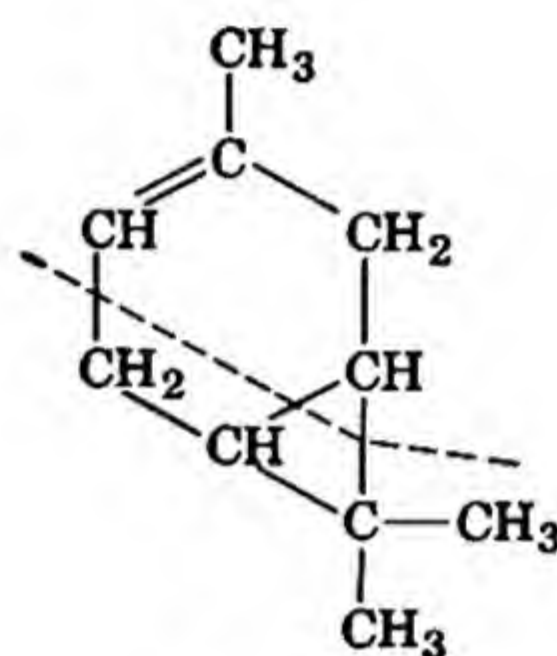
which occurs in many citrus oils, is an example. The bicyclic monoterpenes fall into several groups, depending on the size of the rings. An example of each type is given here.



Thujone

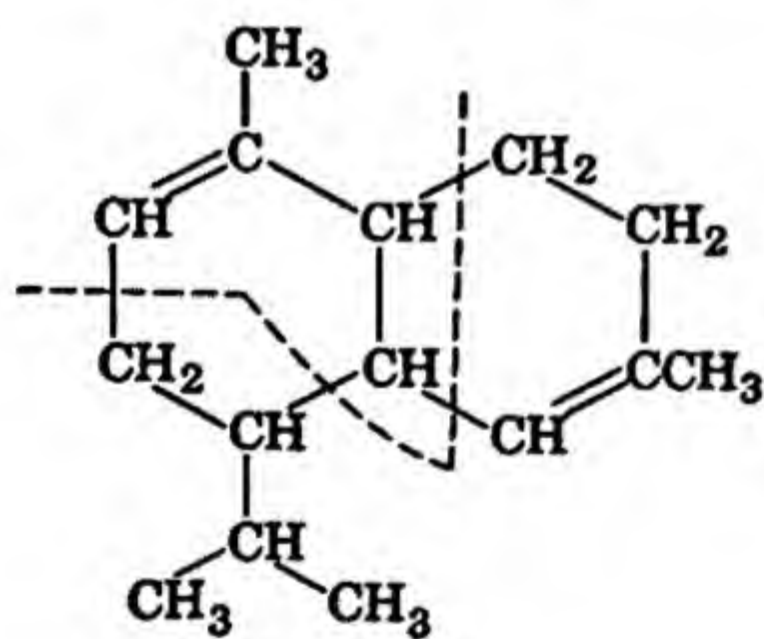


Fenchone

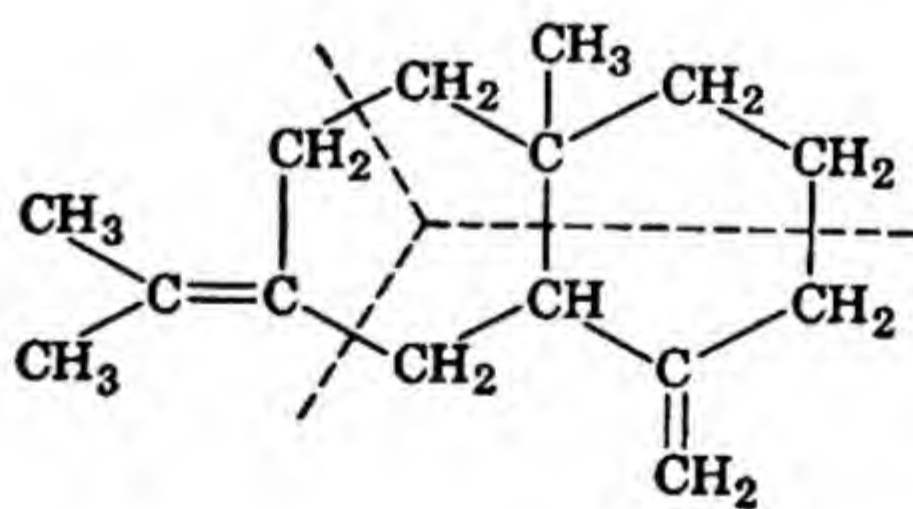


Carene

Of the various types of sesquiterpenes, those having two rings (bicyclic) are the most interesting because of the variety of ring systems that are found. In cadinene, which is a component of cedar and juniper oils, and in selinene, which is present in celery oil, two six-membered rings are fused as in naphthalene (Chapter 6). The



Cadinene

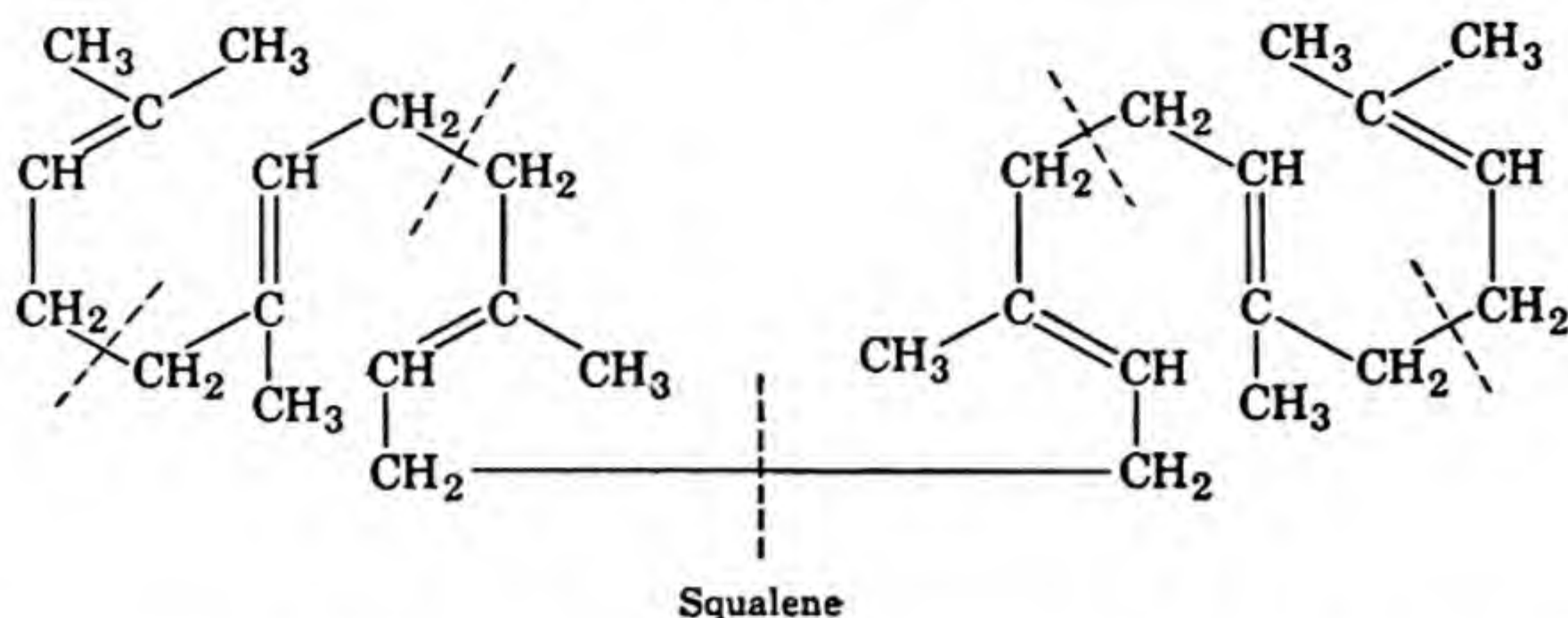


Selinene

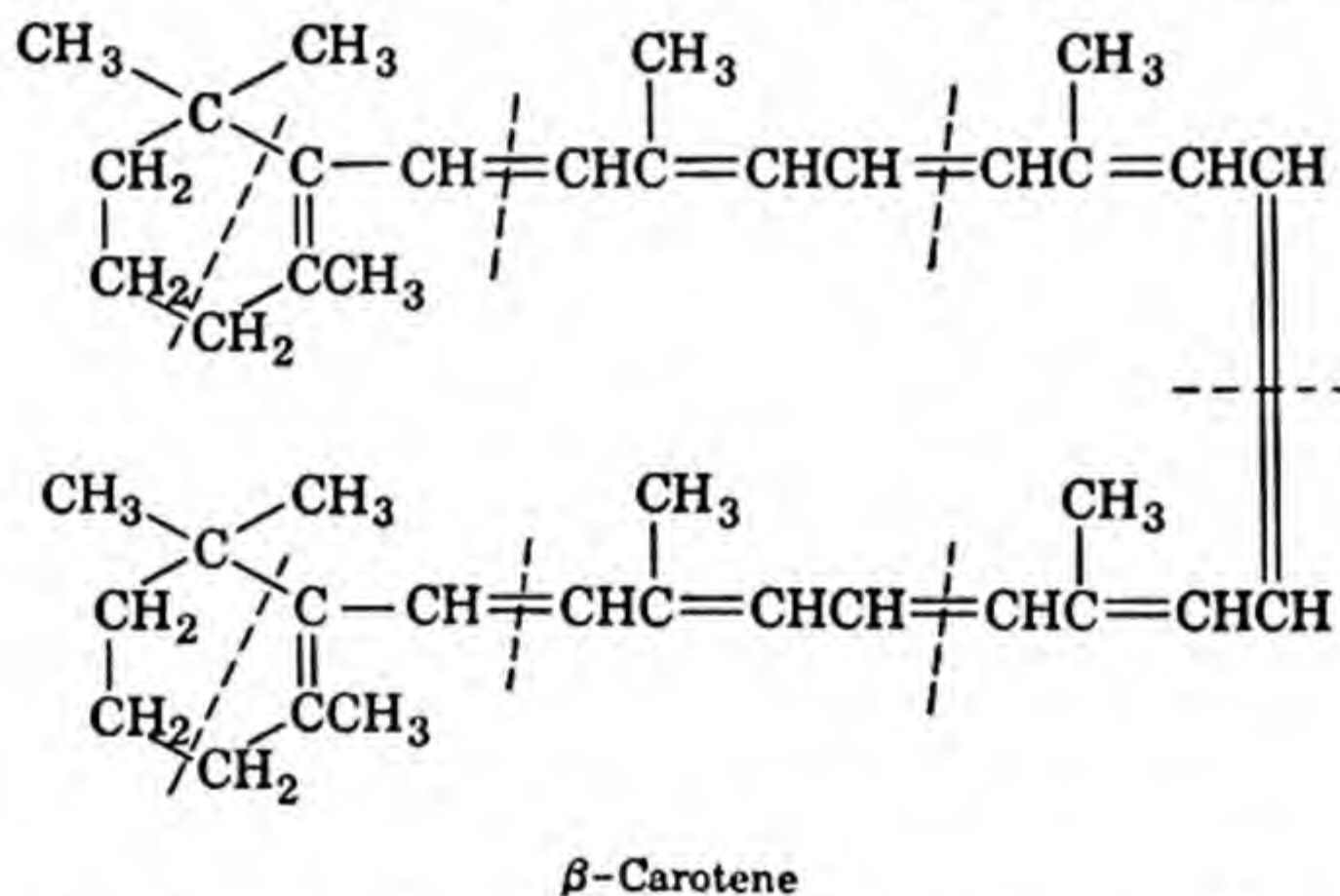
azulenes have a fused system consisting of a seven- and a five-membered ring, and caryophyllene has a nine- and a four-membered ring.

The triterpenes include the open-chain compound squalene found in shark liver oils and believed to be an intermediate in the biological synthesis of steroids (Chapter 7).

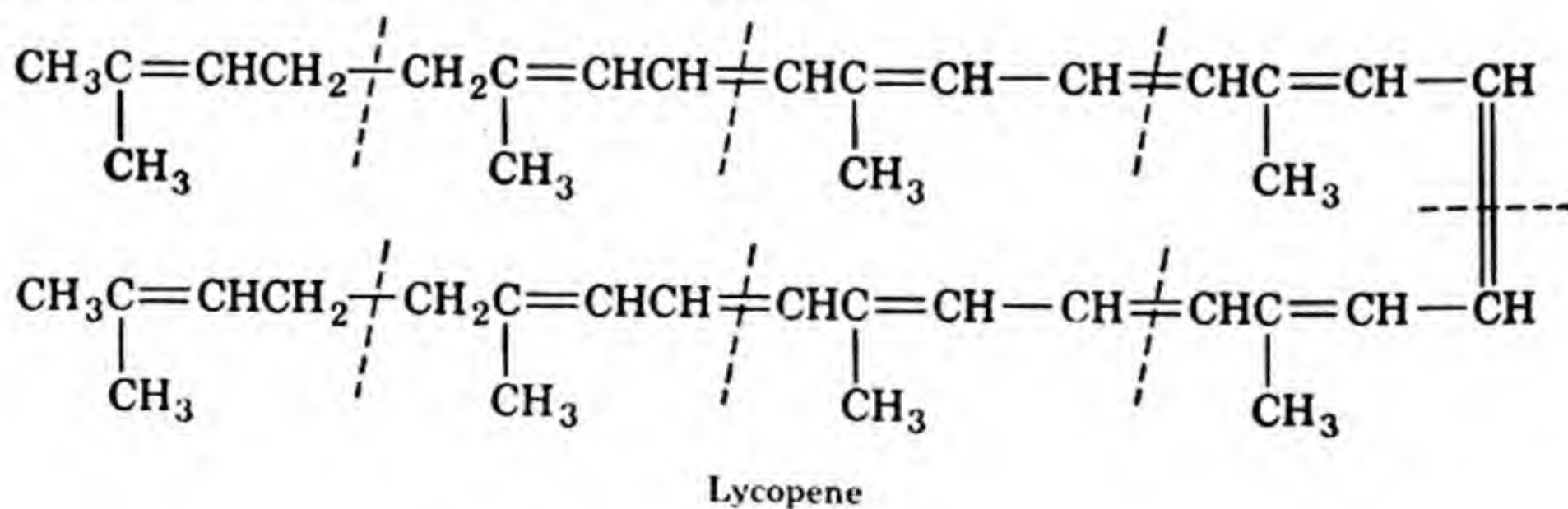




The carotenoids, which are tetraterpenes, are an interesting class of compounds. They are unsaturated hydrocarbons or their oxygenated derivatives. Their color is due to a system of many conjugated double bonds, and the depth of color is dependent upon the number of these linkages. The carotenes are responsible for the color of carrots. They occur also in the leaves of plants, in which their color is normally obscured by other pigments, but as the leaves die in the autumn and the chlorophyll disappears the yellow tints of the carotenes become visible. There are three isomeric carotenes.  $\alpha$ -Carotene differs from  $\beta$ -carotene in the position of the double bond in one of the alicyclic rings; in  $\gamma$ -carotene one of the rings is open and an additional double bond is present. In all of these the carbon skeleton obeys the isoprene rule. Xanthophyll, which is also present



in leaves, is a dihydroxy derivative of  $\alpha$ -carotene. Lycopene, the red pigment of tomatoes, contains eight isoprene units. It differs from the carotenes in that it has no rings.

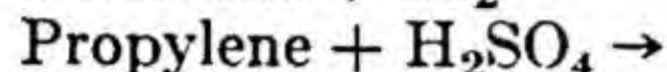
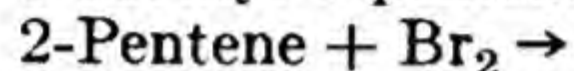
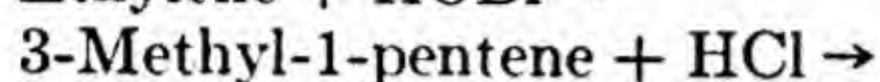
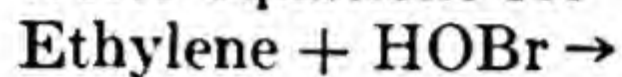


## ► QUESTIONS

1. Write the structures for all the compounds of the molecular formula  $C_5H_8$ .

2. Write the equations for the reaction of isobutylene with bromine, sulfuric acid, hydrogen bromide, and hypochlorous acid.

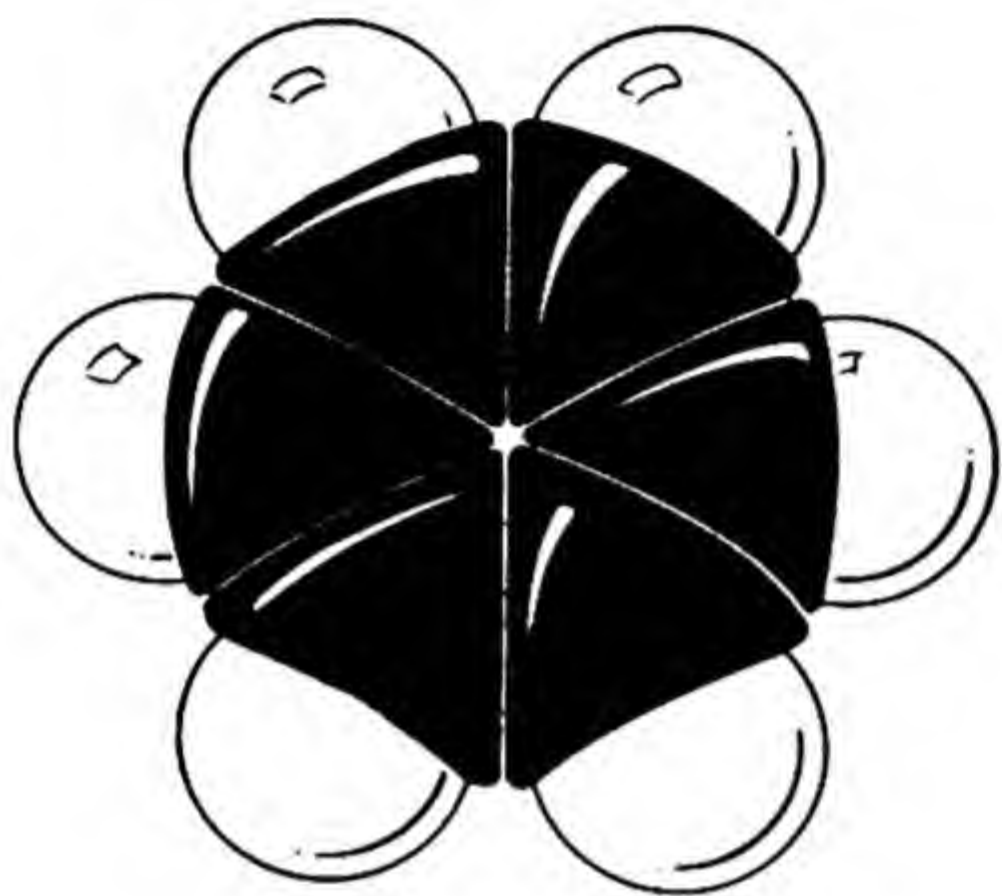
3. Write equations for



4. An analytical method useful in the identification of organic compounds is the quantitative determination of carbon and hydrogen. Thus ethane is composed of 80% carbon and 20% hydrogen, propane, 82% carbon and 18% hydrogen, and butane, 83% carbon and 17% hydrogen. Accordingly, carbon and hydrogen analysis of a pure sample of one of these gases would serve to identify it. Would it be possible to identify a substance known to be ethylene, propylene, or butylene by this method? Explain.



## chapter 6 *Aromatic compounds*

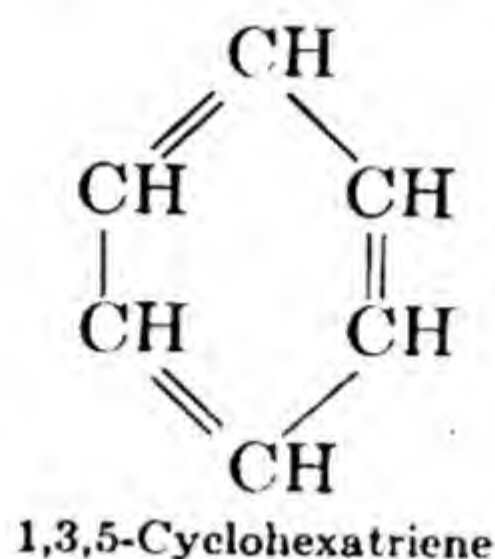


The prototype of aromatic compounds is benzene, a model of which is pictured. The carbon atoms form a six-membered ring, and a single hydrogen atom is attached to each. The linkages between the carbon atoms are identical, and therefore the hydrogen atoms are equivalent.

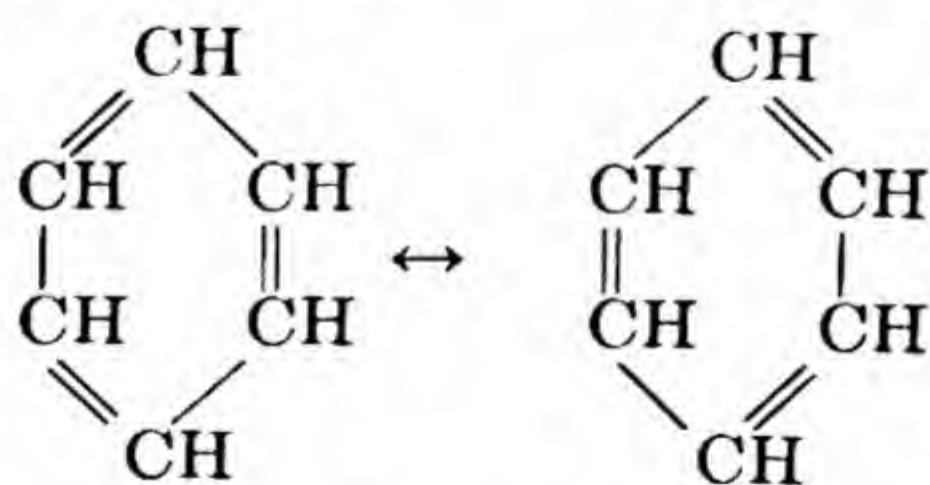
When coal is heated to a high temperature in the absence of air, gases are generated, liquids are distilled, and coal tar, which is volatilized, and coke, the residue, are produced. If the coal tar is fractionally distilled, a large number of substances can be obtained. Among them are the *aromatic* hydrocarbons, such as benzene, toluene, the xylenes, naphthalene, anthracene, and phenanthrene. Though some of the properties of aromatic compounds are like those of the aliphatic substances, some are peculiar and serve to differentiate aliphatic and aromatic compounds. An insight into these differences can best be obtained by an examination of the simplest aromatic compound, benzene.

## ► BENZENE

Benzene is a colorless liquid with the molecular formula  $C_6H_6$ . Of itself this formula would indicate a high degree of unsaturation, since the paraffin hexane is  $C_6H_{14}$ . However, benzene does not readily undergo addition with bromine, and it is resistant to oxidation. Both of these properties are contrary to experience with compounds having multiple bonds. Nevertheless, in 1865 Kekule proposed 1,3,5-cyclohexatriene as the structure of benzene.



This formula has the advantage that all the hydrogen atoms are equivalent, which was also known to be true of benzene, and is supported by the fact that benzene can be reduced to cyclohexane. However, Kekule's formula was objected to violently on the grounds previously mentioned. Kekule later modified his formula by postulating that the benzene double bonds are mobile, but this new formula, as well as some suggested by others, was adjudged unsatisfactory for various reasons. Nowadays it is realized that accurate representation of the structure of benzene by a single classical formula is not possible. However, a number of methods of describing it can be used, one of the most satisfactory of which is an invention called resonance. According to this concept, when the structure of a compound cannot be represented by classical means it is possible to picture it as a hybrid of two or more extreme structures. Thus, using this scheme, benzene can be represented approximately as shown, it being understood that the structure of benzene is an average



of the extreme structures indicated by the double-headed arrow. For a more nearly exact representation of the benzene structure it is

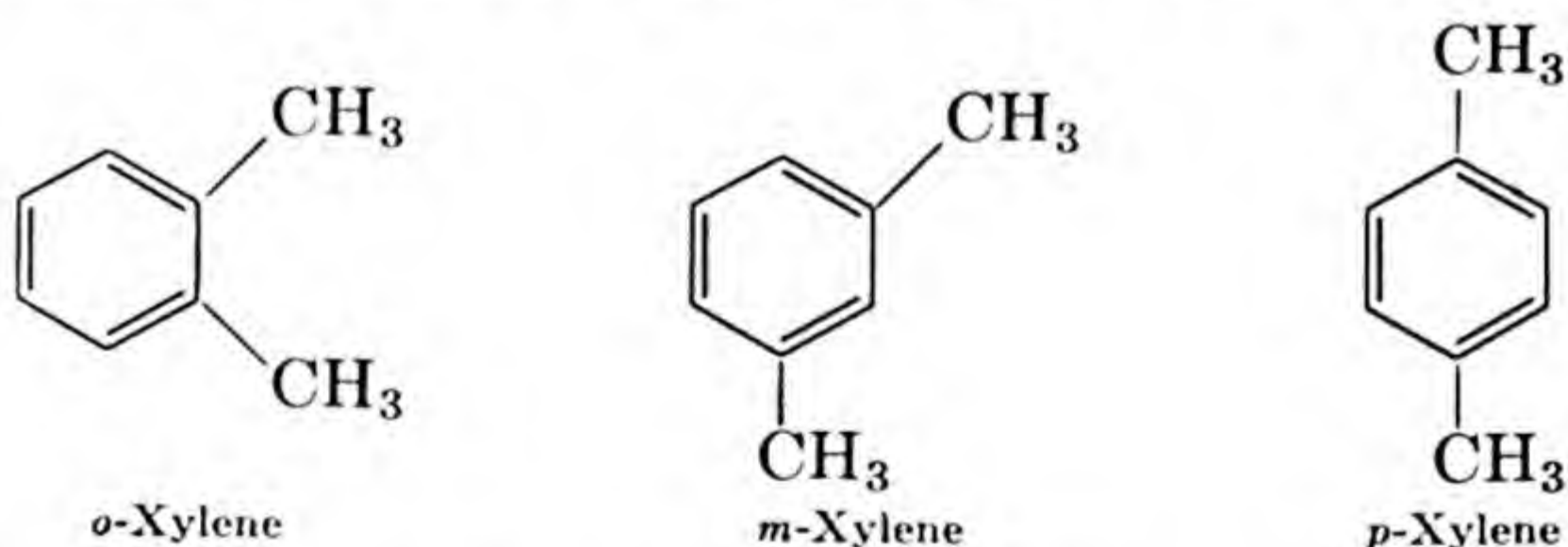


necessary to include other extreme structures, but their contributions are minor. Equilibrium is not intended here; the structures of all benzene molecules are the same. Physical measurements have shown that the six nuclear bonds in benzene are the same length—intermediate between a single and a double bond.

Because the benzene ring is of such common occurrence an abbreviated symbol is used for it; it consists of a hexagon with alternate double and single bonds. Such a formula, though it does not represent reality, is very convenient. The location of the double bonds is not significant so long as they alternate with single bonds in the



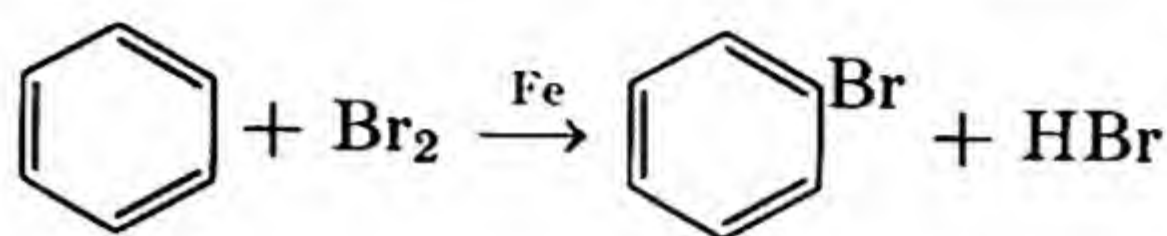
ring. Each corner of the hexagon is meant to represent a CH, unless a hydrogen atom has been replaced by some other group, as in the formula for toluene. Note that when a single group is present in the ring it may be shown as linked to any carbon atom, since all are equivalent. When two groups are attached to the ring, whether they are alike or different, three isomers are possible. If the two groups are linked to adjacent carbon atoms, they are said to be *ortho* (abbreviated in names as *o*-) to each other; when one carbon atom intervenes they are said to be *meta* (*m*-); and when opposite each other, *para* (*p*-). Again the location of the double bonds is not significant so long as they alternate with single bonds.



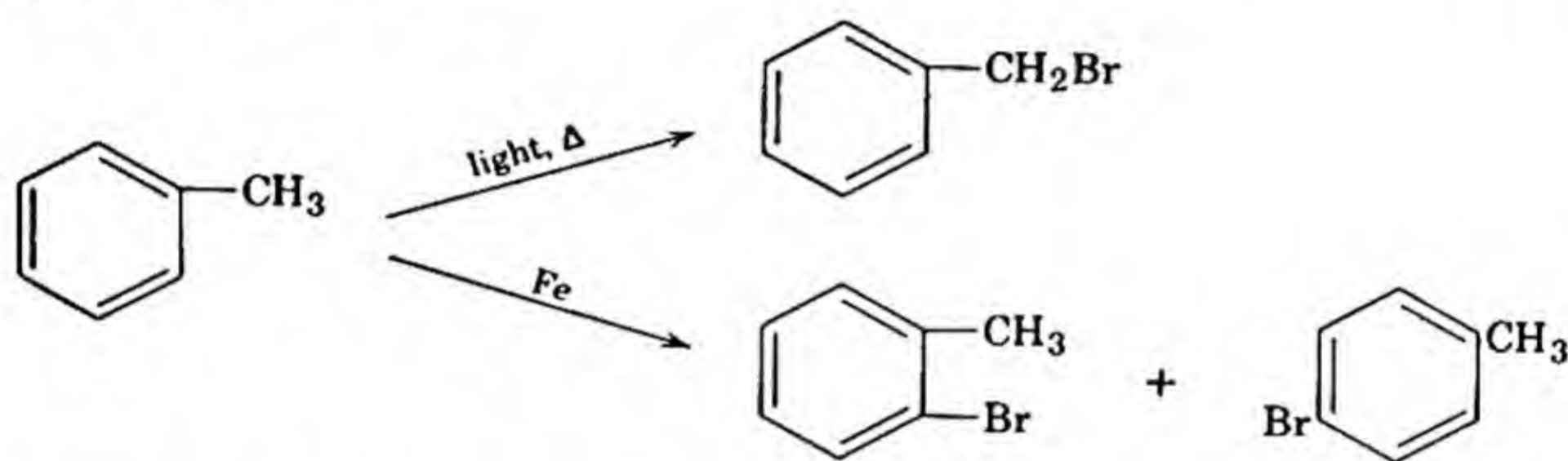
Though the benzene ring undergoes addition only with difficulty, it does readily undergo substitution. This fact, together with the resistance of the ring to oxidation, sets apart the aromatic compounds. The most important of the substitution reactions of benzene are halogenation, nitration, sulfonation, and the Friedel-Crafts reaction.

**Halogenation.** When benzene is treated with chlorine or bromine in the presence of a catalyst, substitution occurs and a molecule of

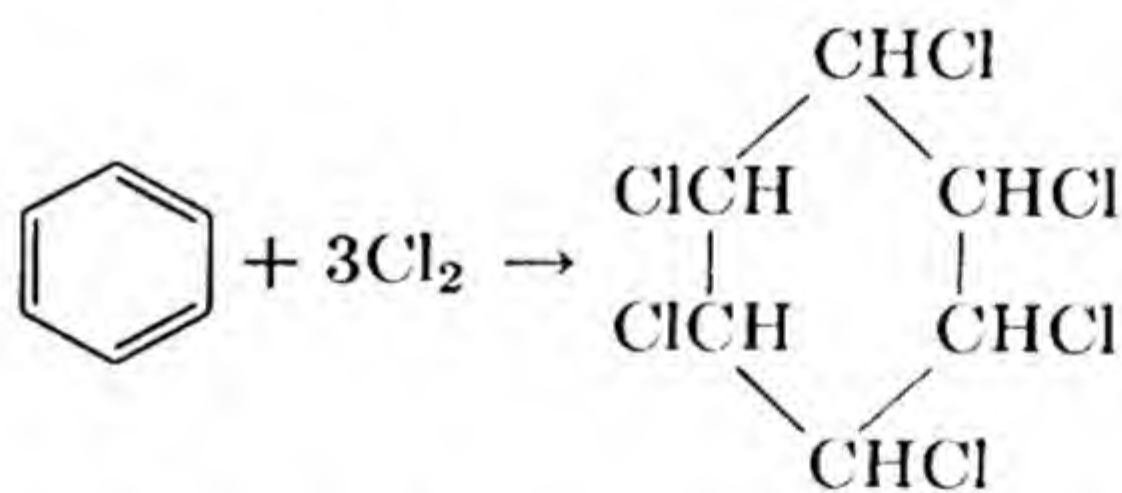




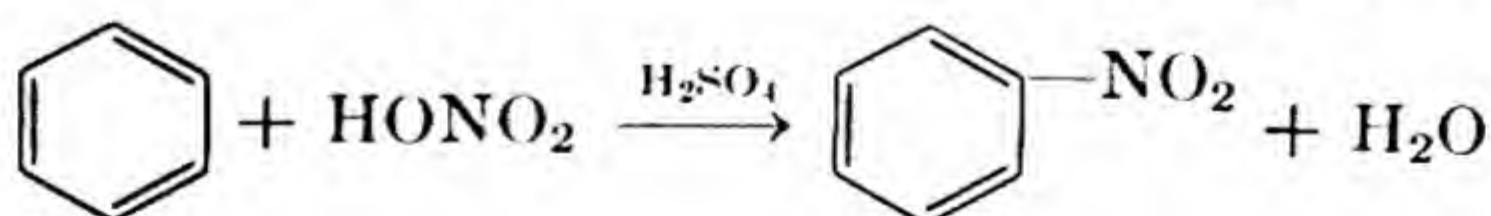
hydrogen halide is evolved. The catalysts are said to be "halogen carriers," for it is believed that their function is to react with the halogen to yield a substance which reacts in turn with the benzene. Aluminum chloride, iron halides, iodine, antimony halides, and metallic iron have been used for this purpose. With toluene, two types of substitution can occur, depending upon conditions, since the hydrocarbon has both an aromatic ring and a saturated aliphatic portion called a side chain.



Addition of chlorine or bromine to benzene occurs if a mixture of the halogen and the hydrocarbon is exposed to a strong light in the absence of a catalyst. The chief products are 1,2,3,4,5,6-hexahalo-cyclohexanes. The mixture of hexachlorocyclohexanes obtained by this process is used as an agricultural insecticide. It is usually called "BHC."



**Nitration.** Introduction of a nitro group ( $-\text{NO}_2$ ) into the benzene ring is often accomplished with a mixture of nitric and sulfuric acids. The nitration of benzene in this manner gives nitrobenzene, a poisonous, slightly yellow liquid which is an important intermediate in the synthesis of numerous useful materials, including dyes and medicinals.

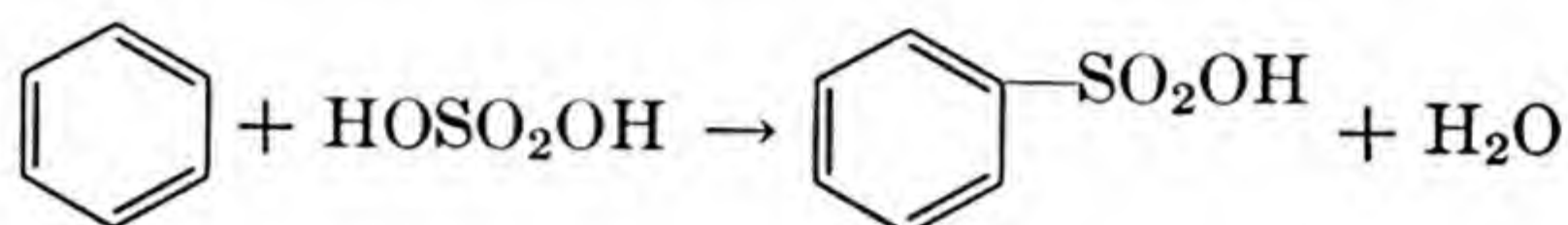


With aromatic compounds more difficult to nitrate, fuming nitric acid, fuming sulfuric acid, or both may be substituted for ordinary



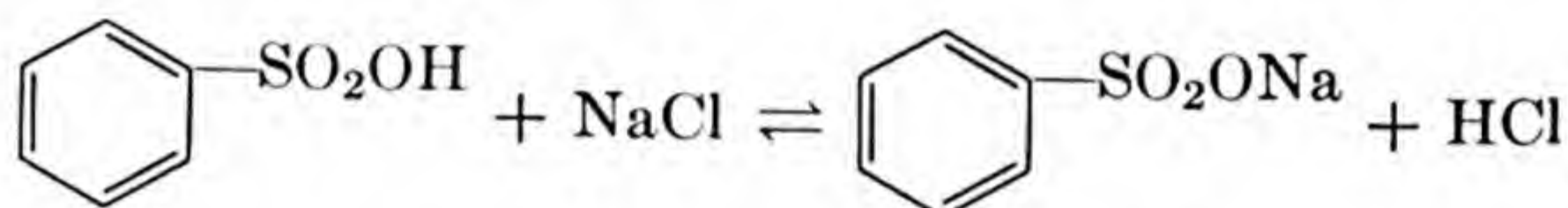
concentrated acids. Most aromatic nitrations proceed at temperatures below  $100^{\circ}$  in contrast to the nitration of paraffins, for which a temperature of  $300\text{--}400^{\circ}$  is required.

**Sulfonation.** Concentrated or fuming sulfuric acid brings about substitution of a sulfonic acid group ( $-\text{SO}_2\text{OH}$ ) in the aromatic nucleus. In general, sulfonation of a given compound requires



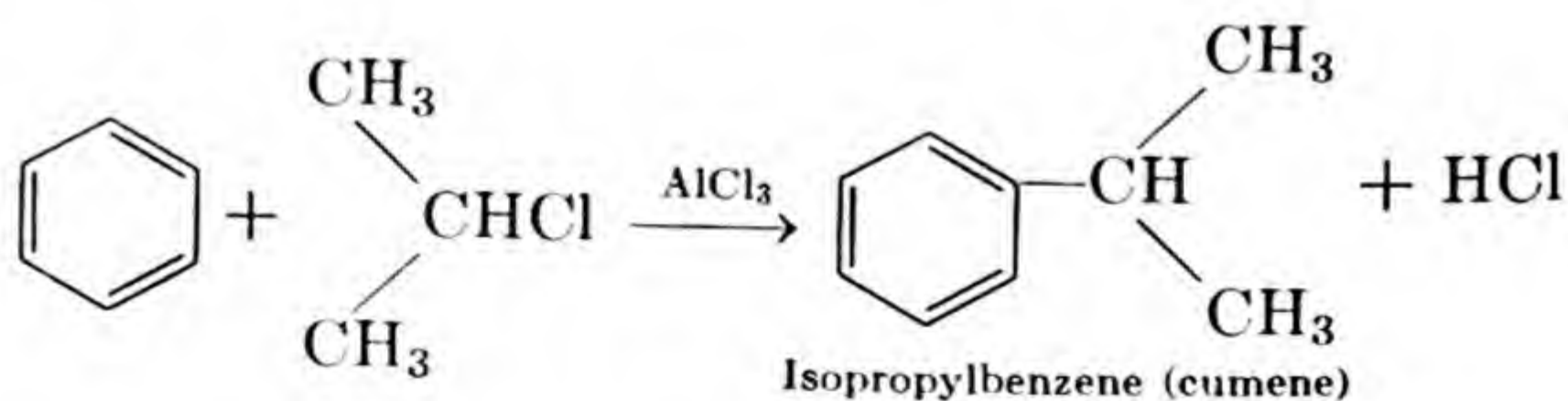
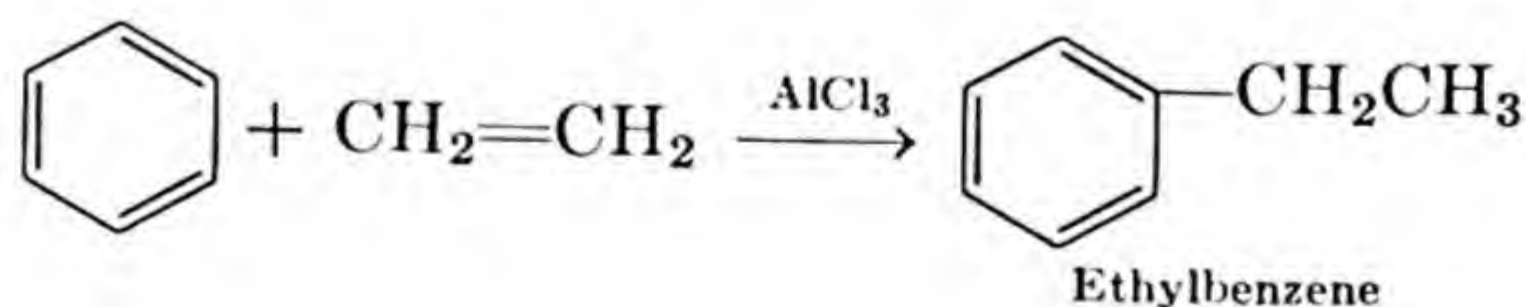
more vigorous conditions than nitration, which is the reason that only nitration is observed when a mixture of nitric and sulfuric acids is used.

Many sulfonic acids are water-soluble and are, therefore, difficult to isolate and purify. They are more often met with as their sodium salts, which can be obtained by treatment of the sulfonation mixture with salt. These salts are very soluble in water but less so in salt

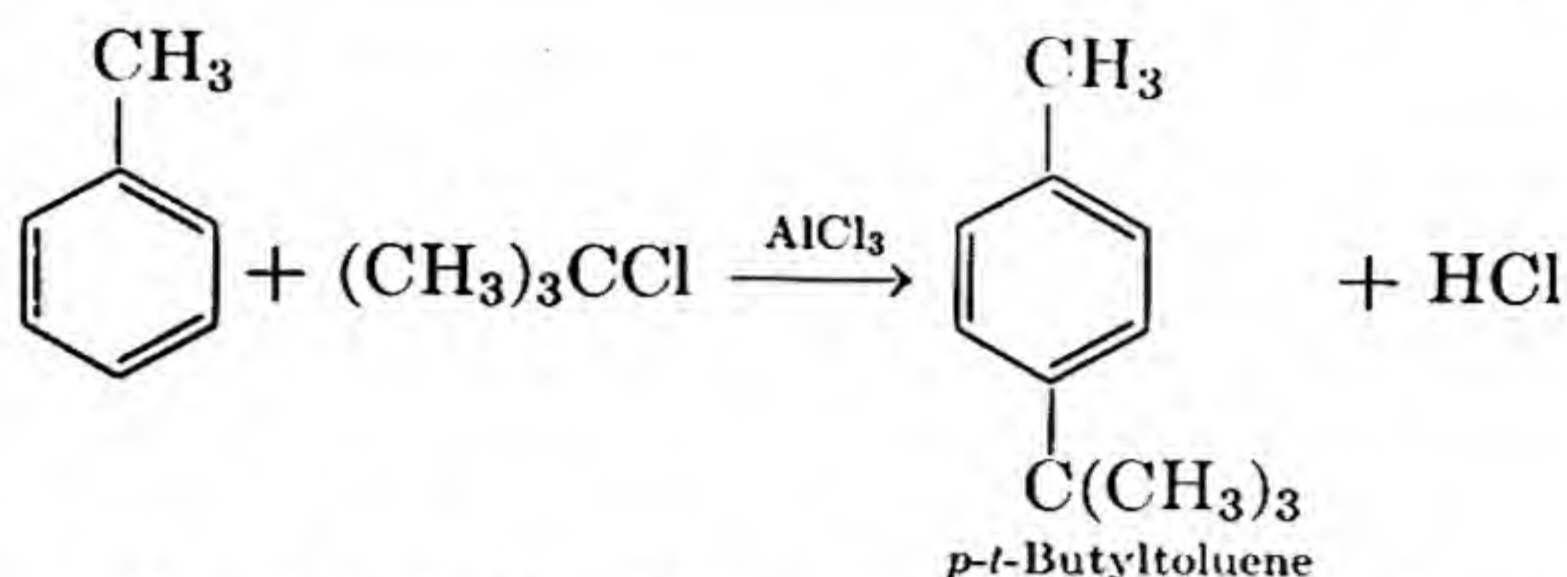


solutions. In dyes and pharmaceuticals water solubility is often necessary. This property can be conferred upon a molecule by sulfonation; that is, the  $-\text{SO}_2\text{OH}$  group functions as a "solubilizing" group. Sulfonic acids partake of the nature of sulfuric acid; they are strong acids and in many instances can serve in place of sulfuric acid.

**Friedel-Crafts Reaction.** Aromatic hydrocarbons undergo reaction with alkyl halides, olefins, or alcohols in the presence of a catalyst such as anhydrous aluminum chloride. The products are alkyl-substituted aromatic hydrocarbons. Unless special conditions are used, a mixture of products is obtained in these *alkylation* reactions because it is difficult to prevent the introduction of more than one



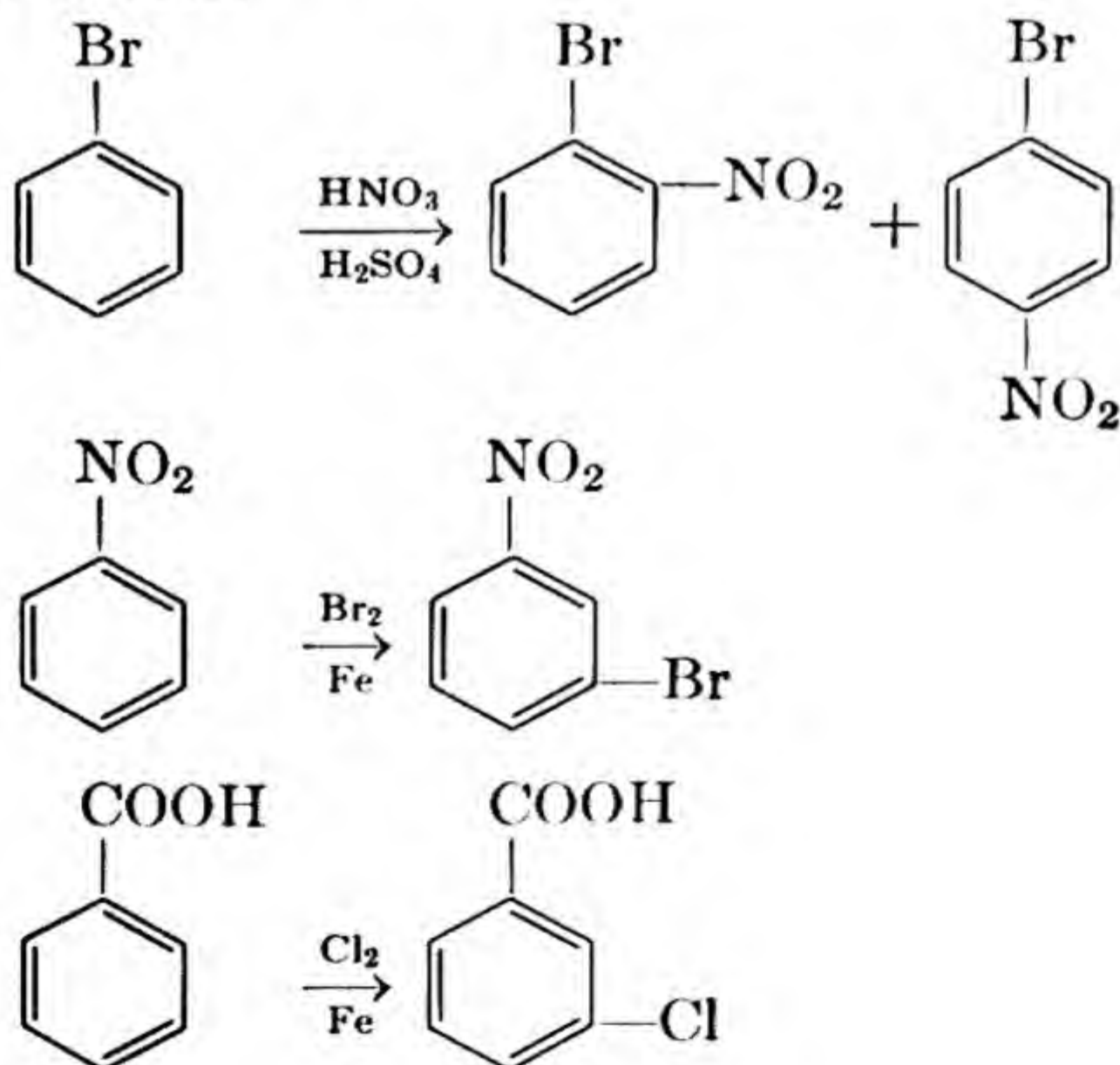




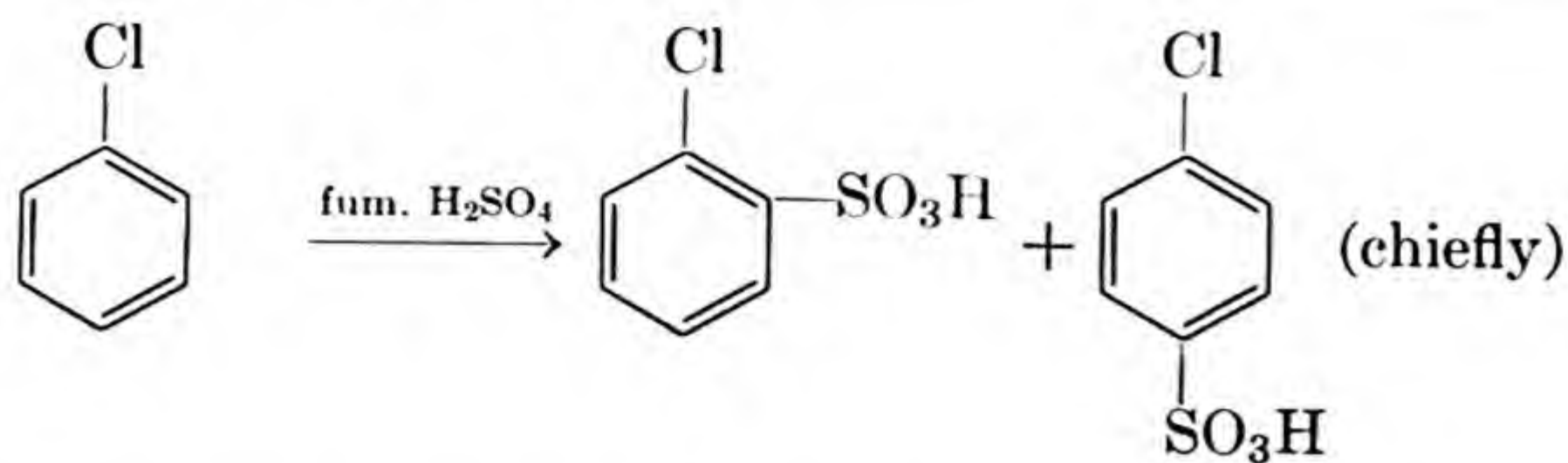
alkyl group. A related Friedel-Crafts reaction is of great value in the synthesis of aromatic ketones (Chapter 9).

**Orientation.** When a group is already present in the benzene ring it would appear that the introduction of a second group could yield three possible isomers. Experience has shown, however, that the position or positions taken by the new group is controlled primarily by the group already present, which can hence be said to have a directing or orienting effect. Substituents can be divided into two large categories on the basis of this property. The *meta* orienting groups direct the entering group *meta* to themselves and have the additional property of making the ring more difficult of substitution. The most common *meta* orienting groups are sulfonic acid ( $-\text{SO}_2\text{OH}$ ), nitro ( $-\text{NO}_2$ ), carboxyl ( $-\text{COOH}$ ), cyano ( $\text{C}\equiv\text{N}$ ), and ketone ( $-\text{C}(=\text{O})\text{R}$ ). The *ortho*, *para* directing groups usually yield

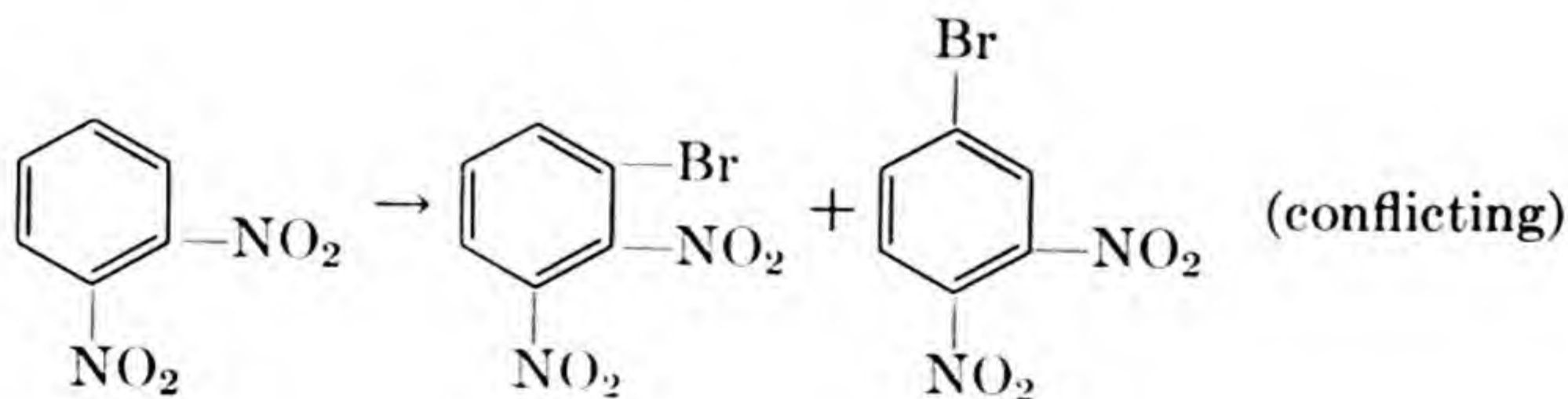
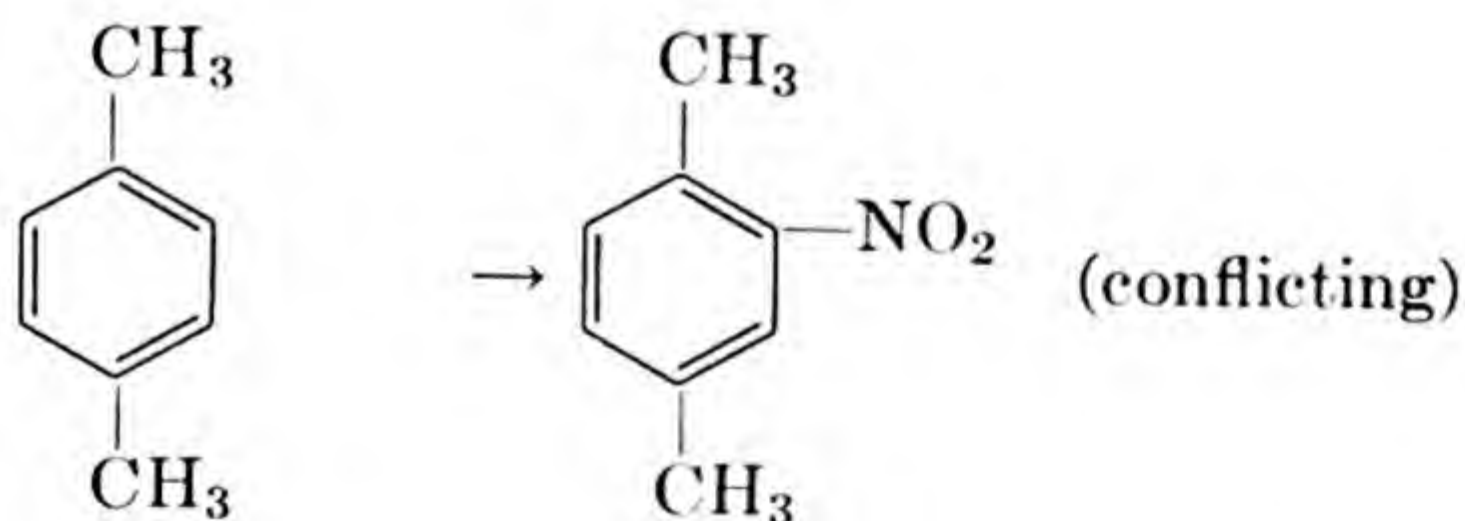
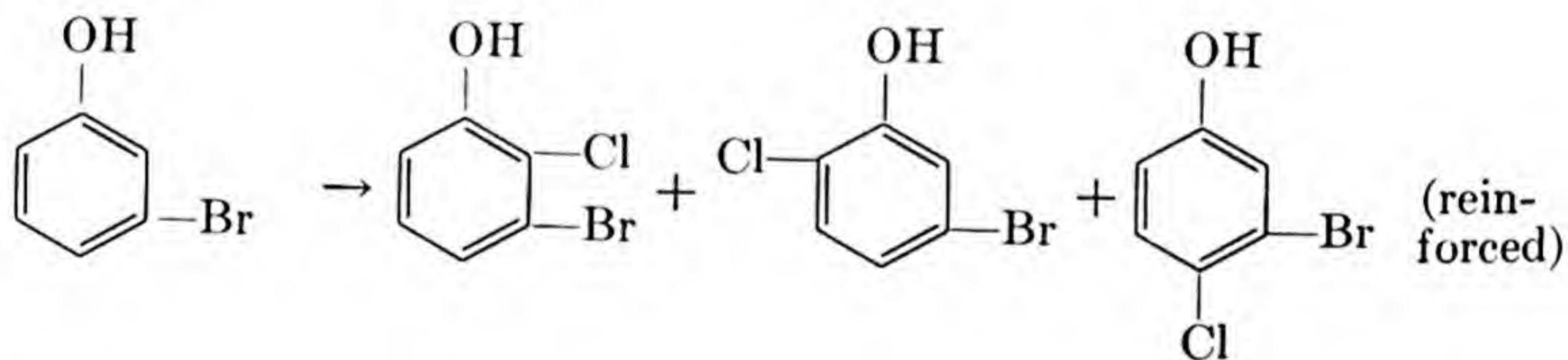
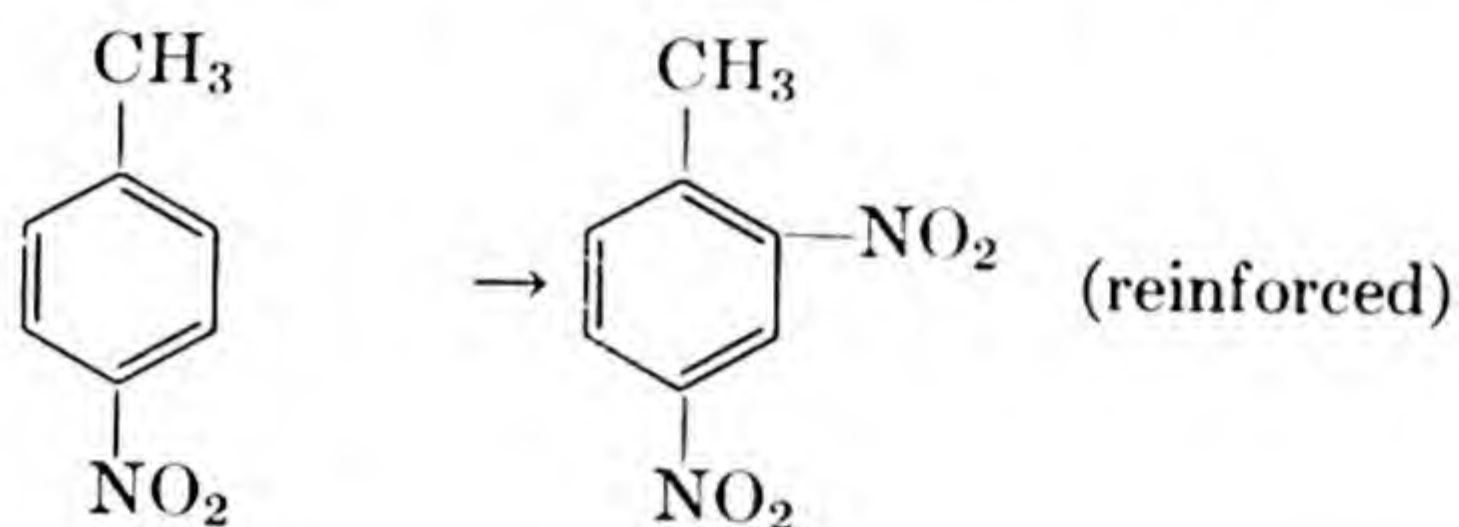
a mixture of the *ortho* and *para* isomers and have an activating effect on the ring. The most frequently encountered groups in this category are alkyl ( $-\text{R}$ ), halogen ( $-\text{X}$ ), amino ( $-\text{NH}_2$ ), hydroxyl ( $-\text{OH}$ ), and ether ( $-\text{OR}$ ). Following are some examples which show these directive effects:

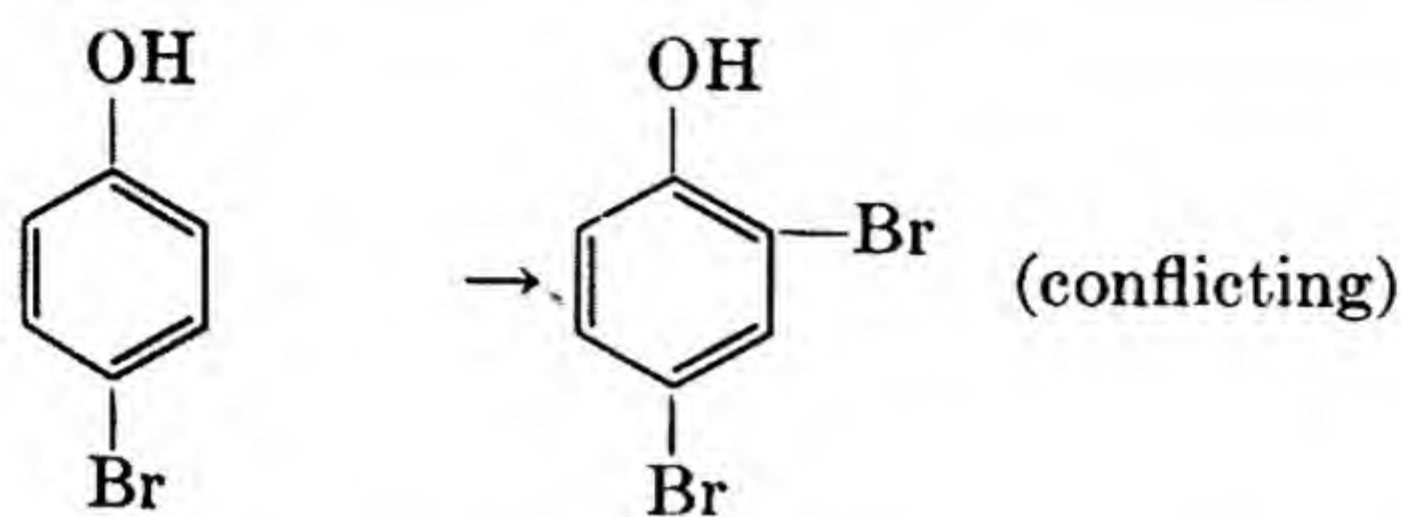






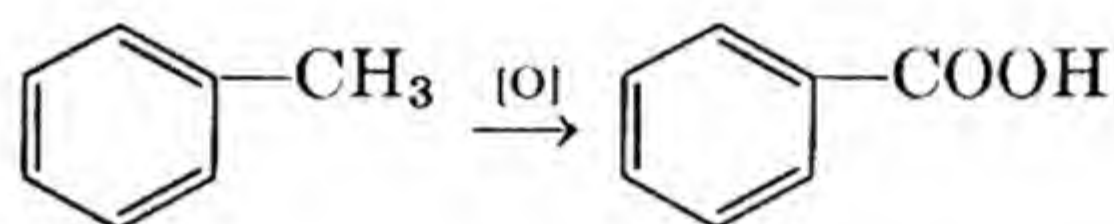
When two groups are present in the benzene ring the introduction of a third follows the same general rules. The directing effects of the groups already present may be reinforcing or conflicting. In the latter case a mixture of isomers is frequently obtained unless the effect of one group is great enough to overcome that of the other. This is often the case when there is an amino or hydroxyl group in the ring, for these groups exert very potent orienting effects.



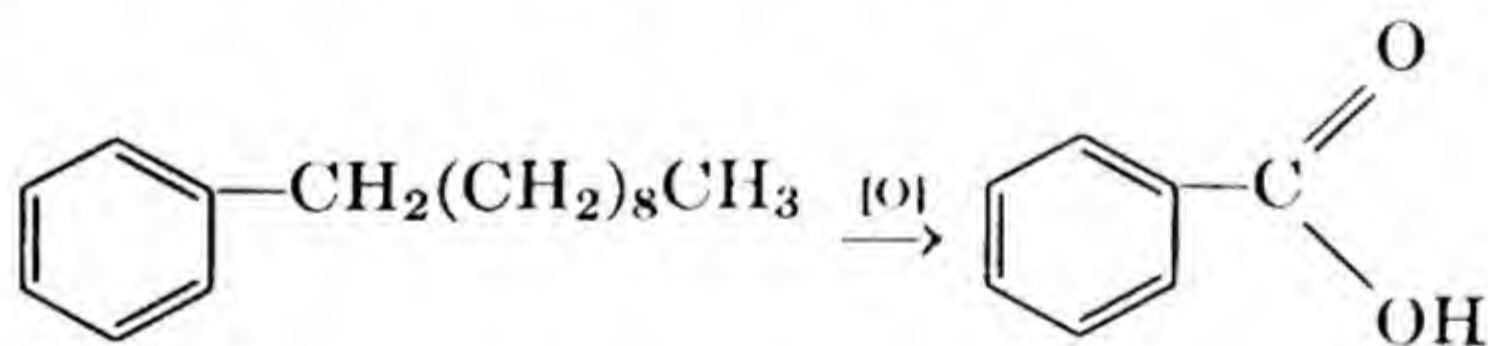


A point to be stressed in connection with such reactions as halogenation, nitration, sulfonation, and the Friedel-Crafts condensation is that groups already present in a ring are seldom displaced by entering groups.

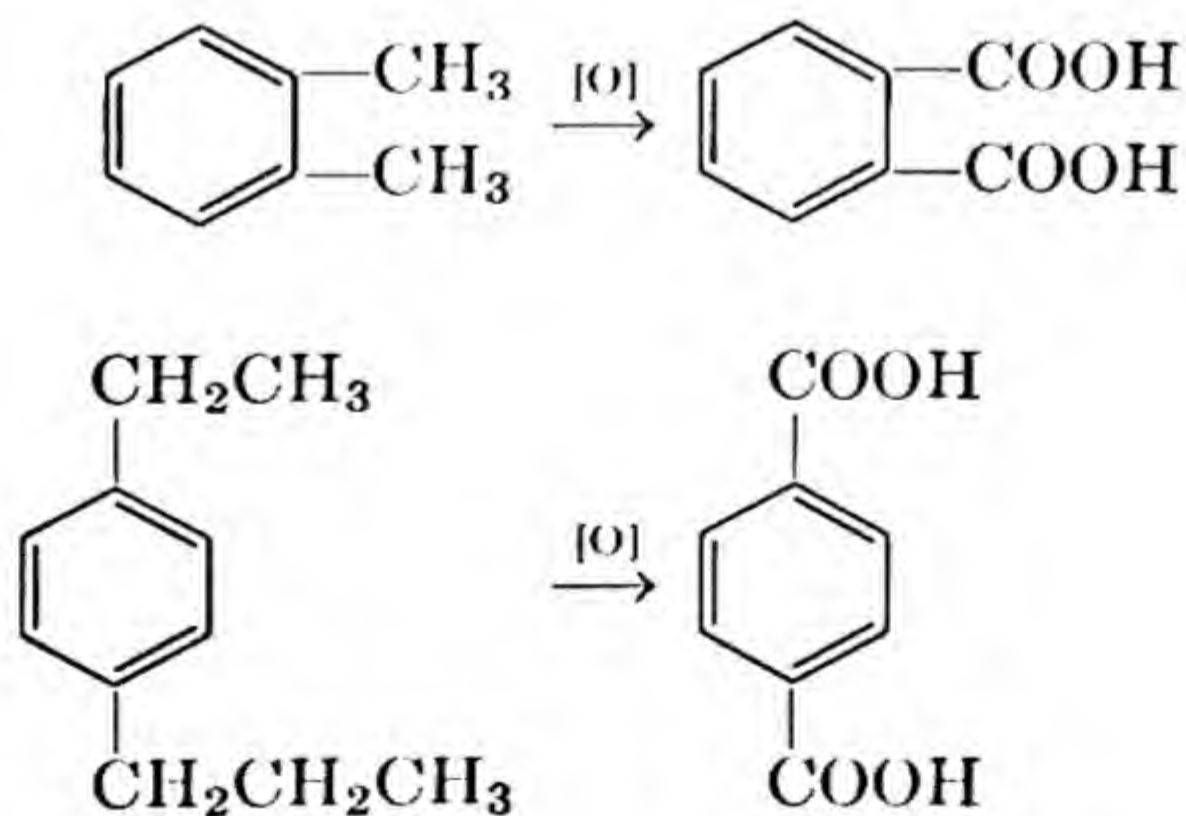
**Side-Chain Oxidation.** The considerable stability of the benzene ring toward oxidation can be illustrated by the conversion of toluene to benzoic acid with a strong oxidizing agent such as alkaline potassium permanganate or chromic acid.



This reaction is general. Benzene derivatives that have a side chain in which carbon is attached directly to the ring are oxidized to benzoic acid, no matter what the length of the chain.



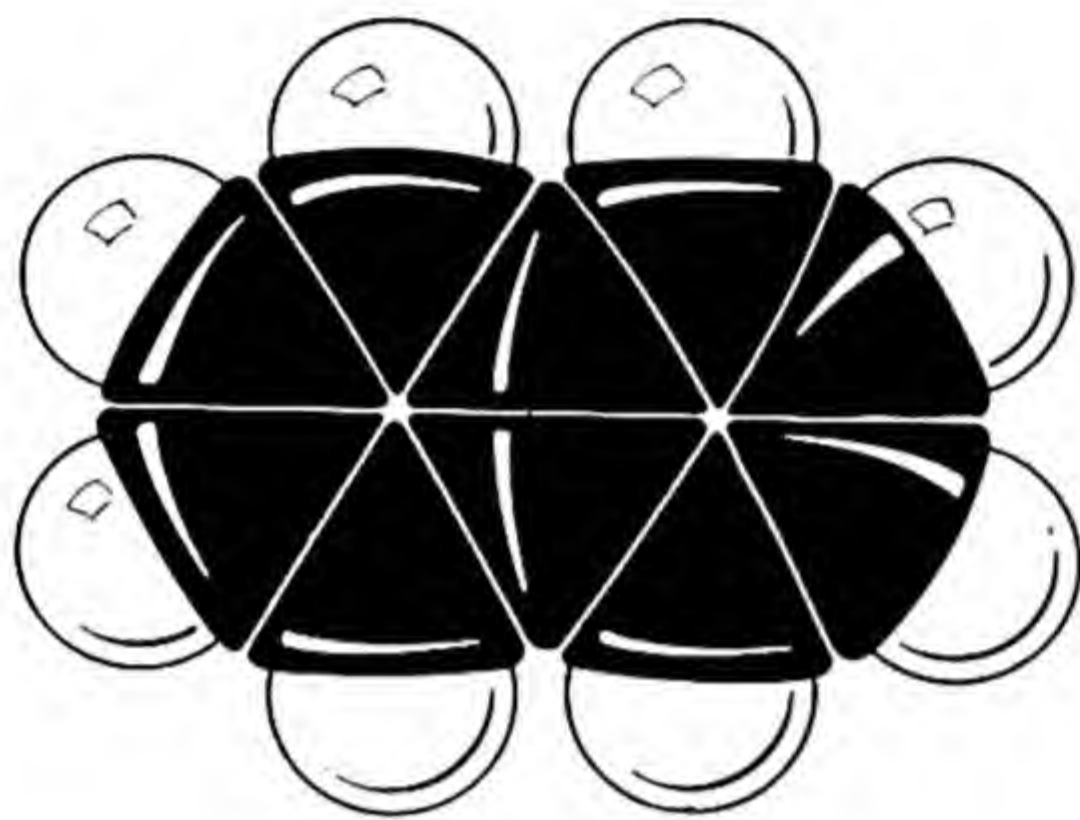
If two such side chains are present, both are oxidized to carboxyl groups.





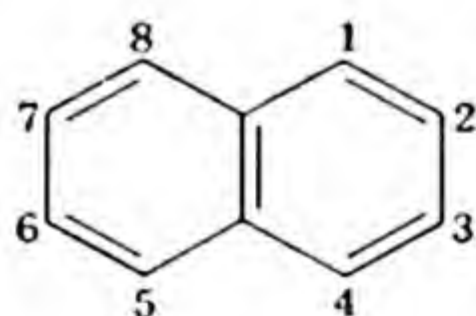
► **CONDENSED AROMATIC HYDROCARBONS**

Coal tar contains hydrocarbons having more than one benzene ring in which two carbon atoms are common to two rings. Such rings are said to be condensed or fused, and the compounds are called condensed aromatic hydrocarbons. The simplest such compound is naphthalene which has two benzene rings. Anthracene and phenanthrene

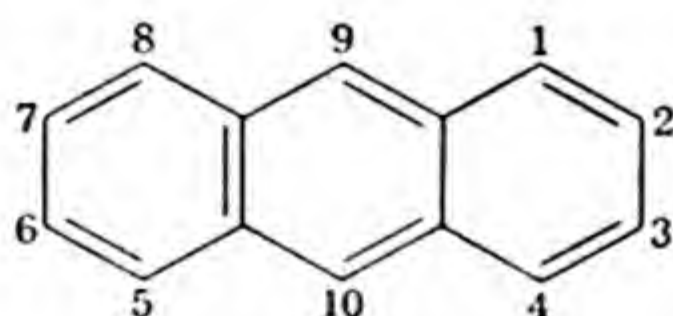


Naphthalene, shown in the model, is a raw material of exceptional importance in the aromatic chemical industry. Coal tar contains more naphthalene than any other single substance.

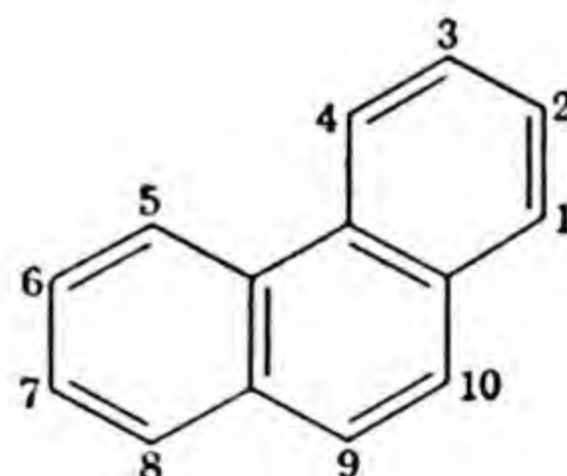
threne each contain three condensed rings. Polynuclear aromatic hydrocarbons are known in which the number of condensed rings is sixteen or more. These compounds undergo reactions much like those of benzene. Though all the hydrogen atoms in benzene are equivalent, more than one monosubstitution product is possible with polynuclear hydrocarbons. Thus in naphthalene two monosubstitution products are possible; the 1,4,5, and 8 positions are equivalent, and the 2,3,6, and 7 positions are equivalent. In anthracene three monosubstitution products are possible ( $1 = 4 = 5 = 8$ ;  $2 = 3 = 6 = 7$ ;  $9 = 10$ ).



Naphthalene



Anthracene



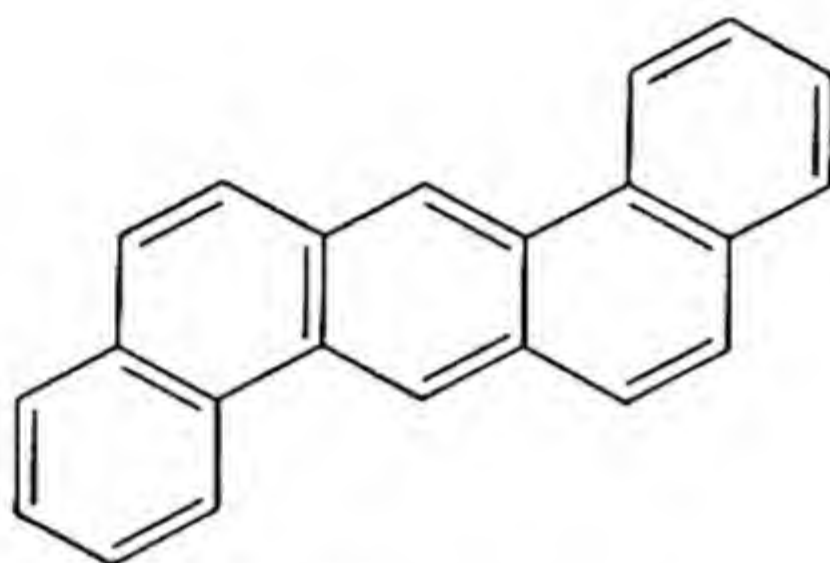
Phenanthrene

The phenanthrene skeletal structure is especially interesting because it is contained in a wide variety of natural products of complex structure, including the opium alkaloids, resin acids, sterols, bile acids, sex and adrenal cortex hormones, heart poisons, and saponins.

Certain more complex polynuclear hydrocarbons, such as 1,2-benzpyrene and 1,2,5,6-dibenzanthracene, are noteworthy because prolonged contact with them may produce skin cancer. Such compounds are said to be carcinogenic.



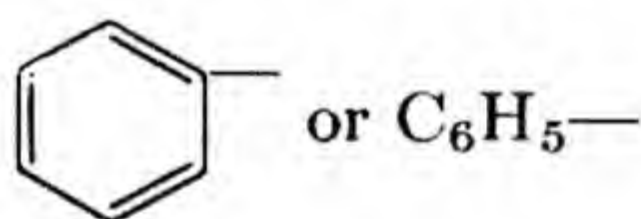
1,2-Benzpyrene



1,2,5,6-Dibenzanthracene

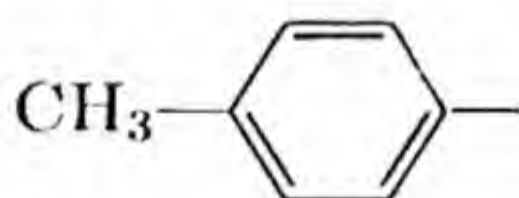
## ► ARYL GROUPS

In the aromatic series the concept of groups is useful in discussion and nomenclature, just as it is with the aliphatic compounds. The formulas and names for some of these groups are



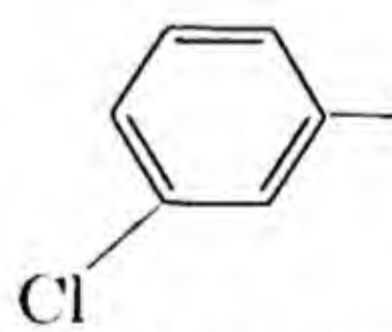
or  $C_6H_5-$

Phenyl

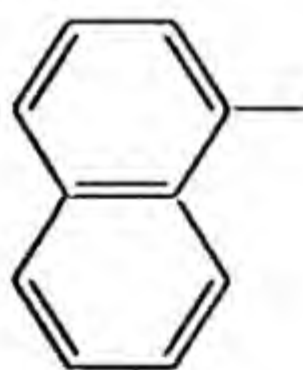


$CH_3-$

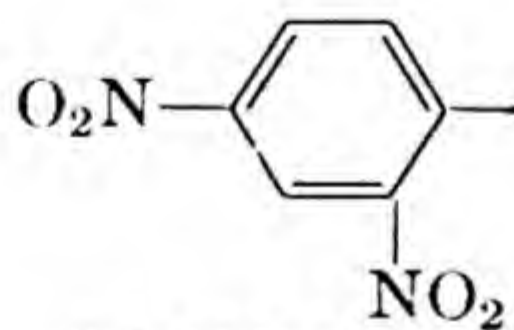
*p*-Tolyl (*p*-cresyl)



*m*-Chlorophenyl



1-Naphthyl



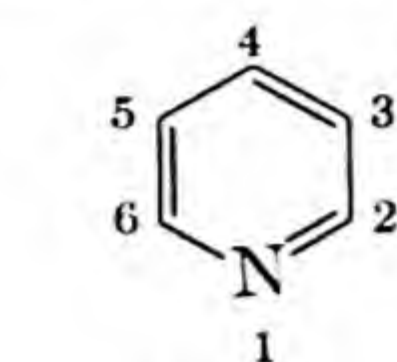
2,4-Dinitrophenyl

## ► HETEROCYCLIC COMPOUNDS

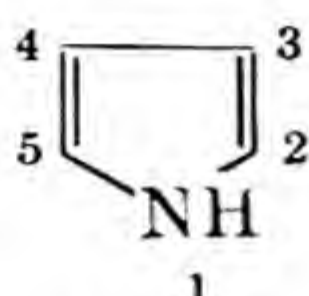
Certain ring compounds are known in which one or more of the atoms comprising the ring are elements other than carbon. Such compounds are said to be heterocyclic (see Chapter 19). Many of



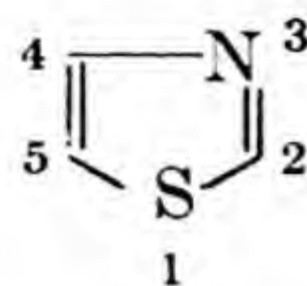
these have aromatic properties. A large number of such ring systems is known, a few of the more important of which are depicted here:



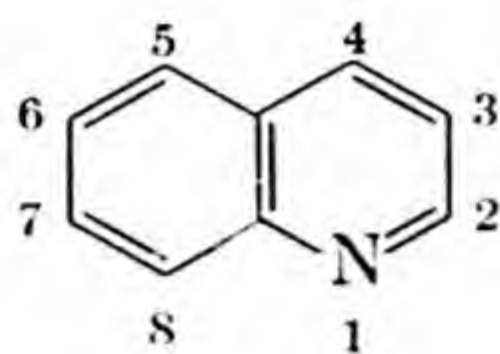
Pyridine



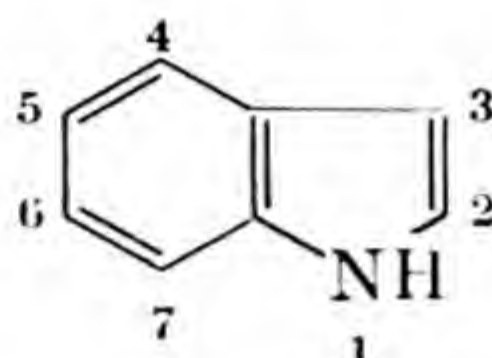
Pyrrole



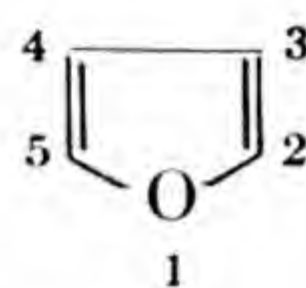
Thiazole



Quinoline



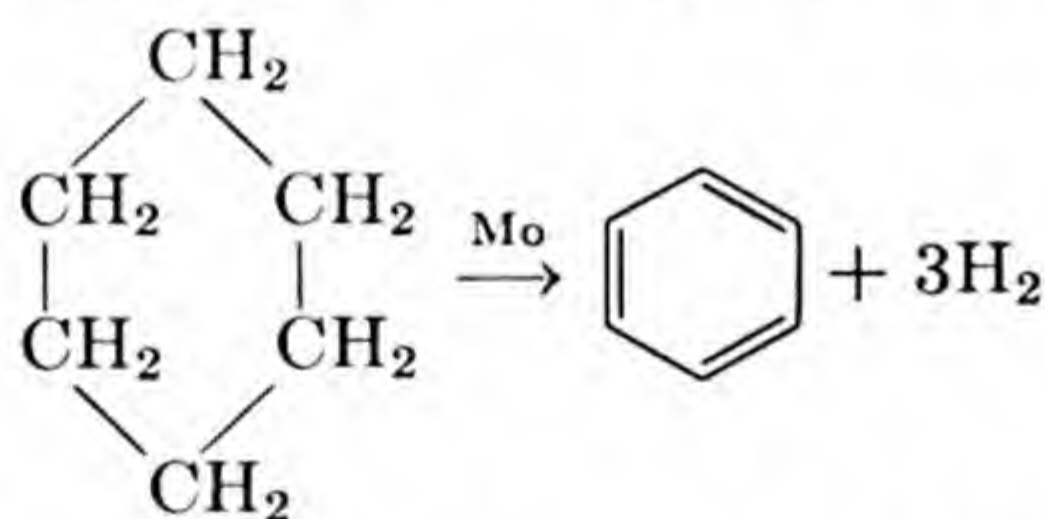
Indole



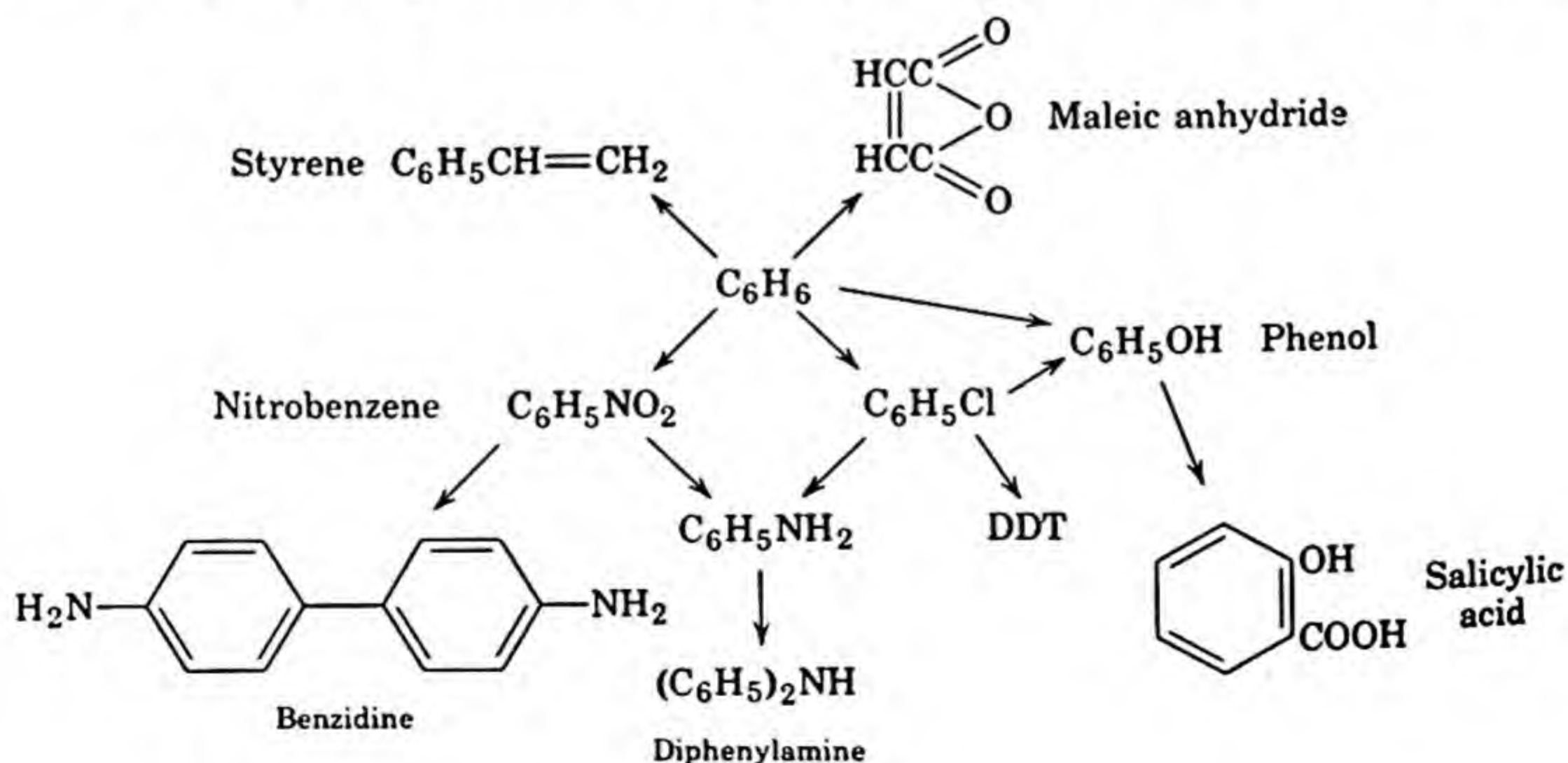
Furan

## ► INDUSTRIAL SIGNIFICANCE OF BENZENE

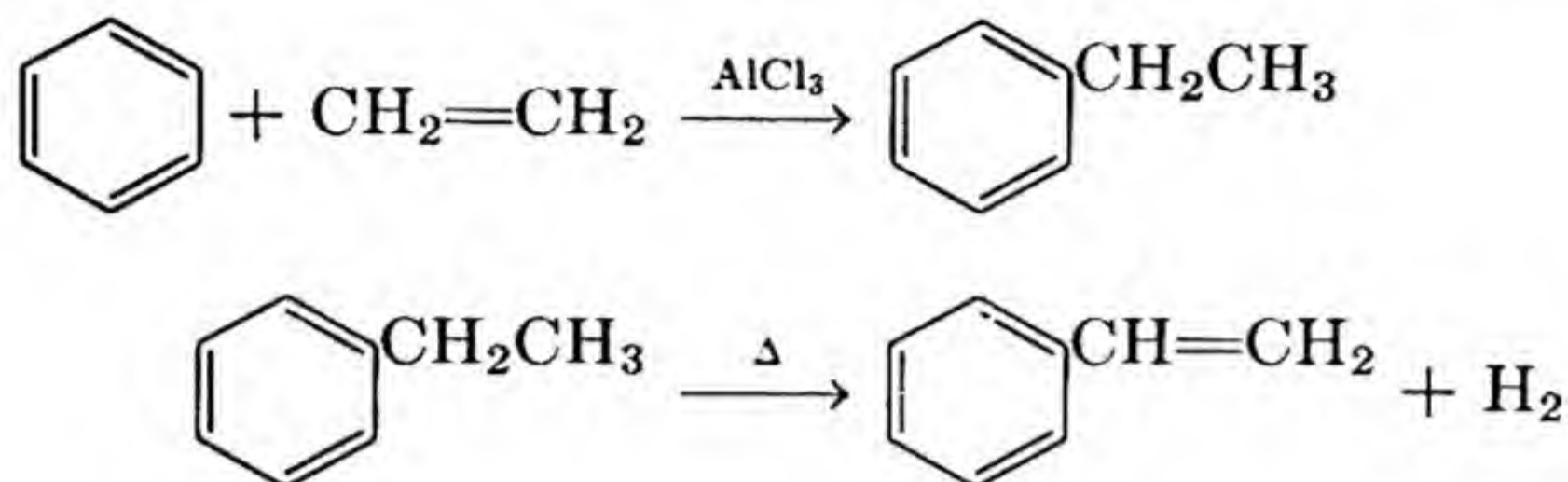
As mentioned previously, benzene is obtained in large quantities from coal tar, but it is also manufactured in enormous amounts from petroleum by the dehydrogenation of cycloparaffins contained therein.



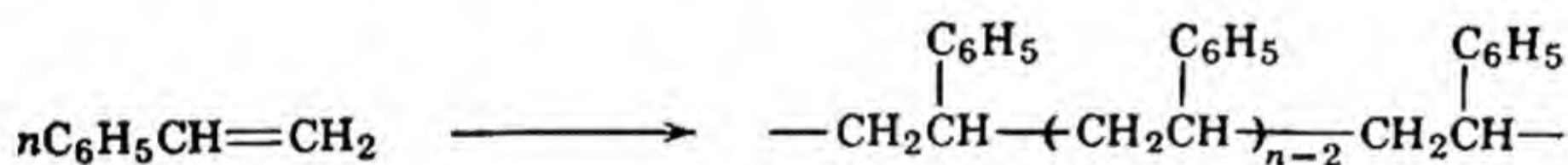
The total annual production of benzene in the United States is more than 200,000,000 gallons. A large quantity goes into blended fuels



for internal combustion engines, and some is applied as a solvent, but most is used in chemical syntheses. A few of the substances which originate with benzene are shown in the chart. Benzene undergoes reaction with ethylene in the presence of aluminum chloride to yield ethylbenzene, which upon pyrolysis furnishes styrene.



Styrene is polymerized on a large scale to yield polystyrene, a useful plastic. Its outstanding properties are hardness, rigidity, resistance to chemical and biological attack, and electrical insulating ability. Its rather sharp melting point allows it to be injection-molded with ease. Large amounts of styrene are copolymerized with butadiene to yield GR-S rubber (Chapter 5).



The other compounds shown in the chart are valuable industrial materials. Consideration is given them in appropriate later chapters.

## ► QUESTIONS

1. How many monosubstitution products of phenanthrene are theoretically possible? Which positions in phenanthrene are equivalent?

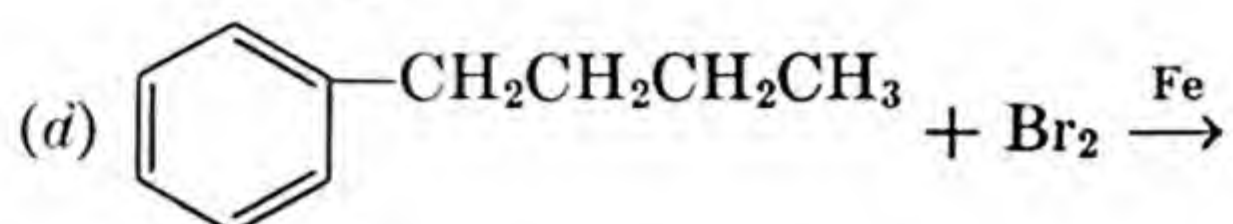
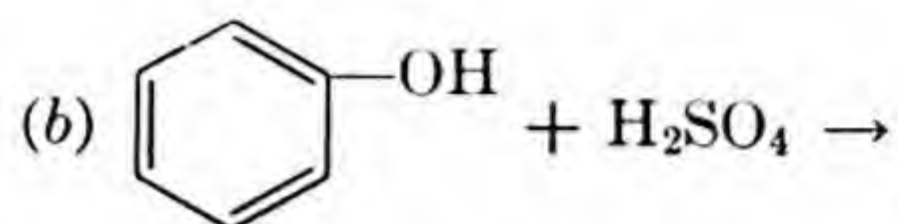
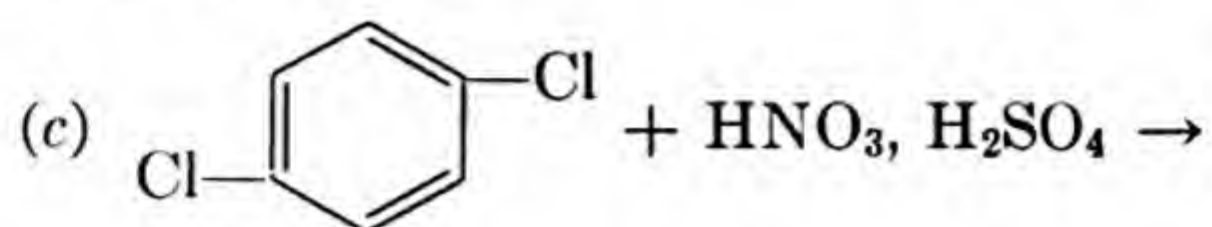
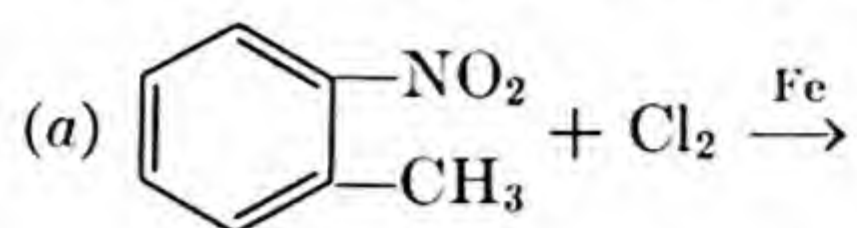
2. TNT (2,4,6-trinitrotoluene) is a military explosive. It is prepared in a three-step process from toluene. Write the equation. For the successive steps in the preparation progressively more vigorous conditions are required. Explain.

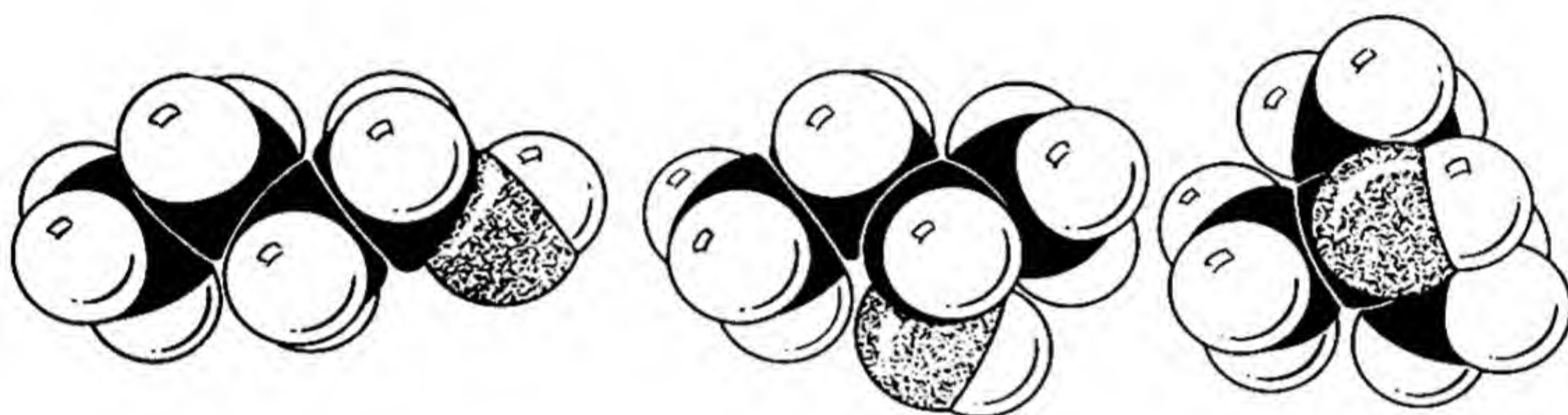
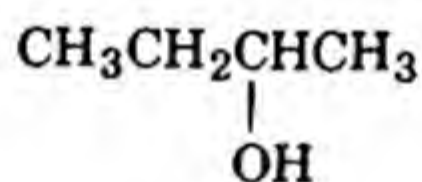
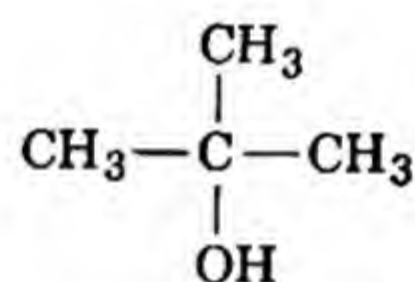
3. Suppose that benzene were brominated successively to the tetrabromo stage. Show by a chart the various substances that are formed and how they are produced.

4. An aromatic hydrocarbon has the molecular formula  $\text{C}_9\text{H}_{12}$ . Write all the possible structural formulas with names and show how each would behave if it were heated with alkaline permanganate.



5. Show by equations the following reactions:



*n*-Butyl alcohol*sec*-Butyl alcohol*t*-Butyl alcohol

The models show three of the isomeric butyl alcohols,  $\text{C}_4\text{H}_9\text{OH}$ . *n*-Butyl alcohol is primary, *sec*-butyl alcohol is secondary, and *t*-butyl alcohol is tertiary. The crowding around the central carbon atom of *t*-butyl alcohol is apparent in the model.

The simple alcohols constitute a homologous series having the general formula  $\text{C}_n\text{H}_{2n+1}\text{OH}$ . They may be considered derivatives of paraffin hydrocarbons in which the hydrogen atom has been replaced by a hydroxyl group. The hydroxyl group is the functional group of the alcohols and is responsible for their characteristic properties.



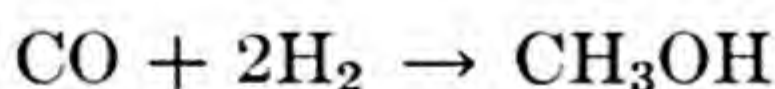
The table shows some examples of the series:

Alcohols			
Formula	Common Name	Systematic Name	Class
$\text{CH}_3\text{OH}$	Methyl alcohol	Methanol	1°
$\text{CH}_3\text{CH}_2\text{OH}$	Ethyl alcohol	Ethanol	1°
$\text{CH}_3\text{CH}_2\text{CH}_2\text{OH}$	<i>n</i> -Propyl alcohol	1-Propanol	1°
$\text{CH}_3\text{CHCH}_3$   OH	Isopropyl alcohol	2-Propanol	2°
$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$	<i>n</i> -Butyl alcohol	1-Butanol	1°
$\text{CH}_3\text{CHCH}_2\text{CH}_3$   OH	<i>sec</i> -Butyl alcohol	2-Butanol	2°
$\text{CH}_3\text{CHCH}_2\text{OH}$   CH <sub>3</sub> CH <sub>3</sub>	Isobutyl alcohol	2-Methyl-1-propanol	1°
$\text{CH}_3\text{COH}$   CH <sub>3</sub>	<i>t</i> -Butyl alcohol	2-Methyl-2-propanol	3°
$\text{CH}_3\text{CHCH}_2\text{CH}_2\text{OH}$   CH <sub>3</sub>	Isoamyl alcohol	3-Methyl-1-butanol	1°

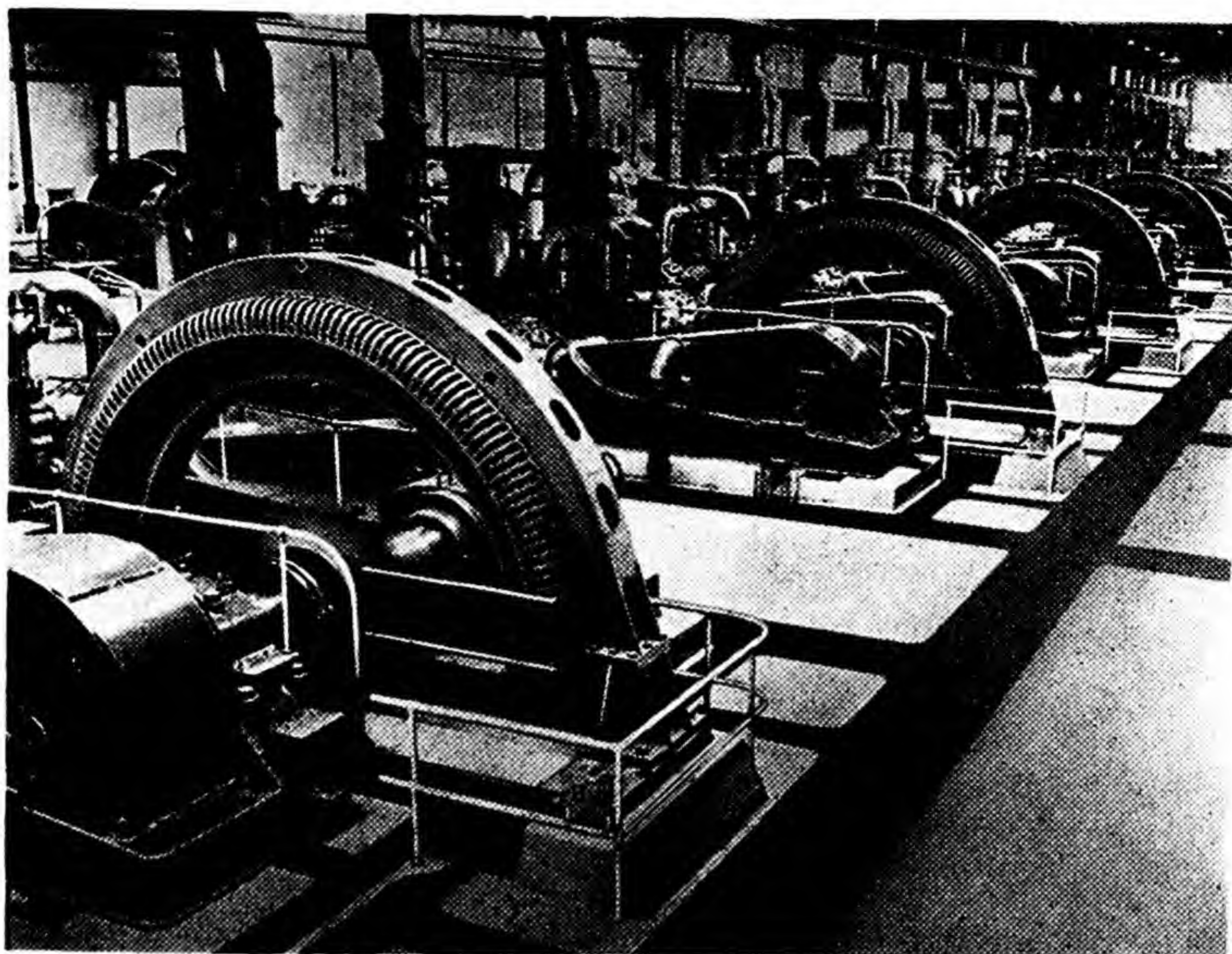
Because the properties of the various types differ to some extent alcohols are classified as primary (1°), if they contain the  $\text{—CH}_2\text{OH}$  group, secondary (2°), if they contain the  $\begin{array}{c} \diagup \\ \text{CHOH} \\ \diagdown \end{array}$  group, and tertiary (3°), if they have the  $\begin{array}{c} \diagdown \\ \text{—COH} \\ \diagup \end{array}$  group. These classifications are also useful in naming the alcohols. In the systematic nomenclature the hydroxyl group is accorded the ending “-ol,” and, if necessary, a locating number is used.

## ► PREPARATION OF ALCOHOLS

Methanol is obtained by the reaction of carbon monoxide and hydrogen at a high temperature and pressure and in the presence of a catalyst containing oxides of copper and of other metals. Ethyl, *n*-propyl, and isobutyl alcohols are obtained as by-products; the







A battery of compressors employed in high pressure commercial operations such as the synthesis of ammonia, methanol, urea, and propionic acid. High pressure gas-phase reactions are carried out only infrequently in the laboratory but are common in industry. (Photograph courtesy of the Du Pont Company.)

amounts of these relative to methanol can be increased by modification of the catalyst. A small amount of methanol is obtained by the dry distillation of wood.

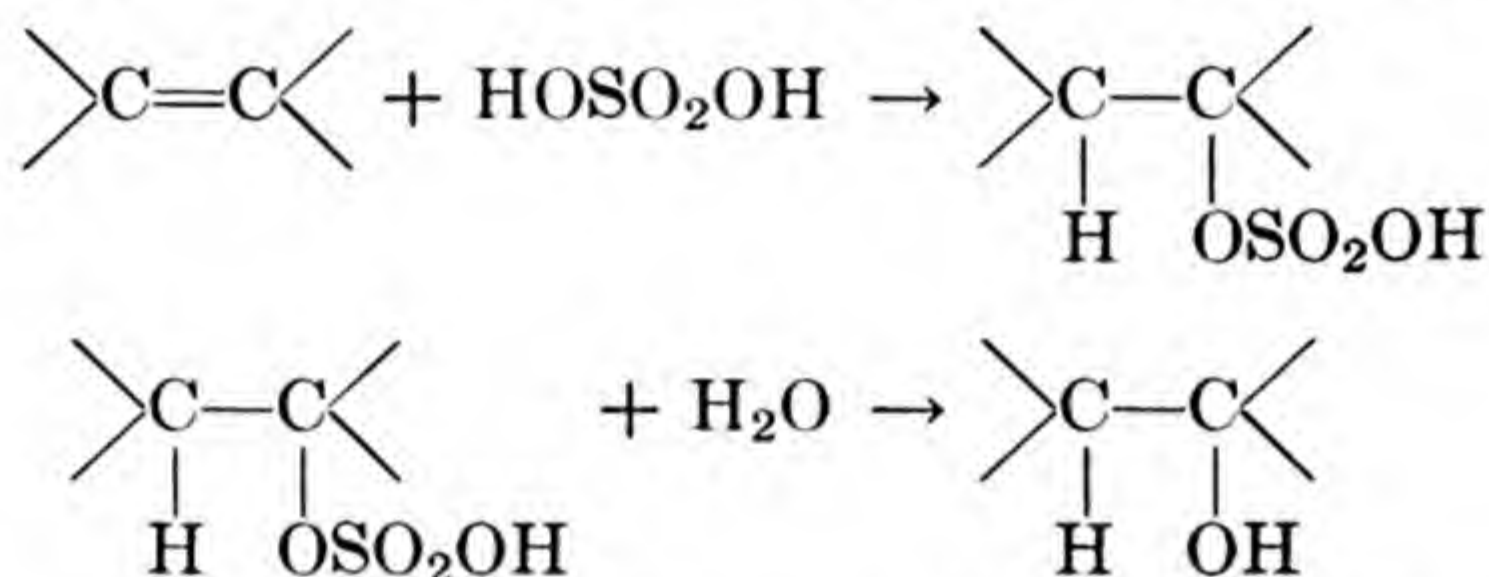
Ethyl alcohol is produced by the fermentation of starch or sugar-containing materials. If grain or potatoes are used, the starch therein must first be converted into maltose (a sugar). This can be effected by the action of malt, which contains the enzyme diastase. The production of alcohol from sugar is accomplished with a yeast which produces the enzyme zymase. With molasses, which is primarily sugar, the first step is unnecessary. The product is an aqueous solution of ethyl alcohol (up to 18%) together with small amounts of higher alcohols, especially isoamyl. To obtain higher concentrations of ethyl alcohol it is necessary to distil the mixture. The maximum concentration which can be obtained in this way is 95%, a "constant-boiling" mixture. So-called absolute alcohol is anhydrous;



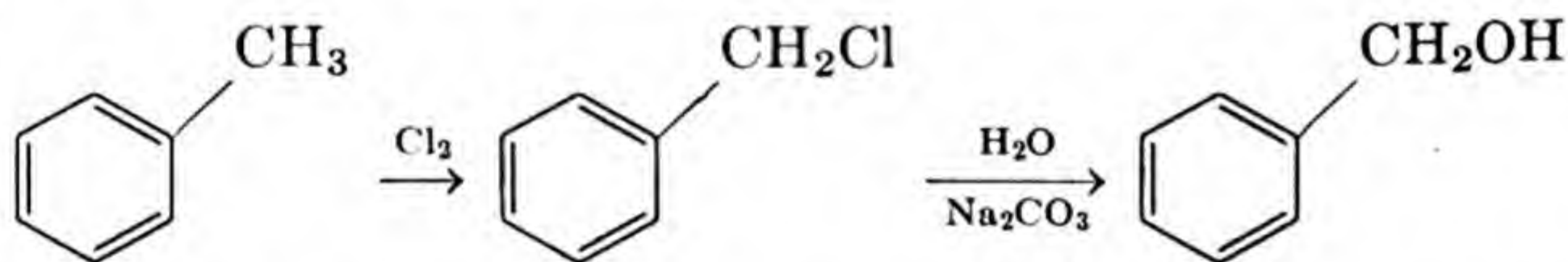
it is prepared by fractional distillation of a mixture of 95% alcohol and benzene. Under these conditions a new constant-boiling mixture composed of alcohol, water, and benzene distils at a lower temperature than any of the components. Absolute alcohol remains as the residue.

*n*-Butyl alcohol has also been made by a fermentation process with starch as the substrate. The organism used is *Clostridium acetobutylicum*, a bacterium, and the products, in addition to *n*-butyl alcohol, are acetone and ethyl alcohol.

Olefins from the cracking process have become an important source of alcohols. Ethyl alcohol (from ethylene), isopropyl alcohol (from propylene), and *t*-butyl alcohol (from isobutylene) are made commercially either by the catalytic addition of water to the olefin or by the addition of sulfuric acid and hydrolysis of the product.



An additional method for obtaining alcohols consists in the treatment of alkyl halides with water in the presence of a base. This procedure is used for benzyl alcohol. The reaction is not of general



value, however, since alkyl halides are usually made from alcohols. Benzyl alcohol, a mild surface anesthetic, is a component of ointments used to relieve itching.

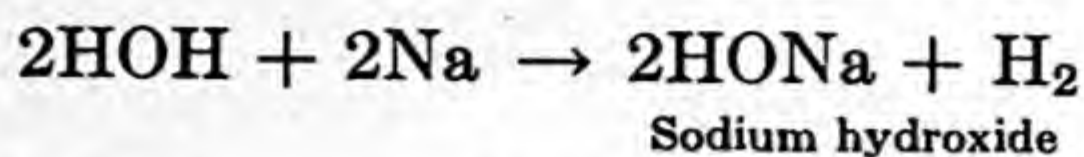
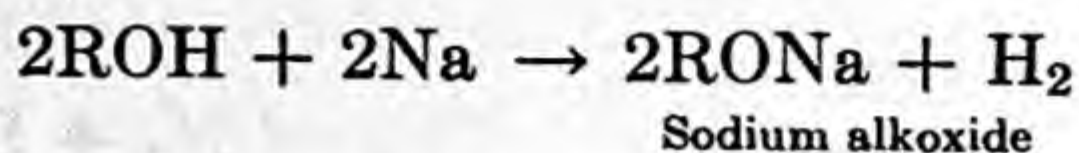
The synthesis of complex alcohols is often accomplished in the laboratory by the reaction of a Grignard reagent with an aldehyde, a ketone, or an ester (Chapter 9).

## ► REACTIONS OF ALCOHOLS

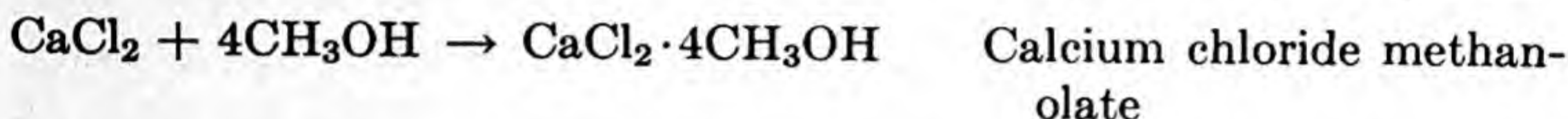
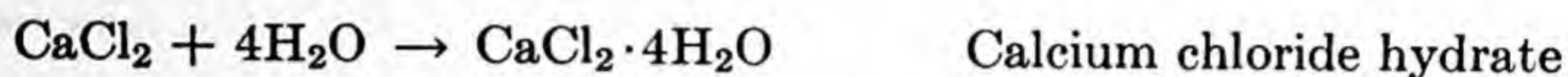
A comparison of the structures of water and the alcohols shows that the alcohols may be considered alkyl derivatives of water, and, indeed, some of their reactions are similar to those of water. For



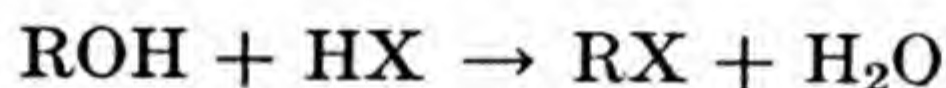
example, active metals such as sodium and potassium replace the hydroxyl hydrogen.



The evolution of hydrogen makes this reaction useful as a test for alcohols. Another reaction of the lower alcohols which is like that of water is the formation from certain salts of alcoholates which are similar in structure to the hydrates.

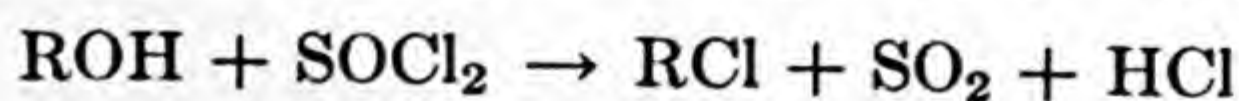
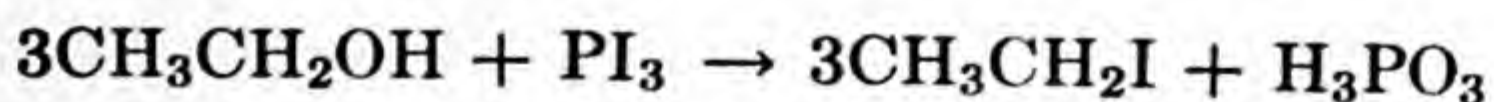


Alcohols react with various acids with the liberation of water. Of the reactions of this kind, those involving the hydrogen halides are most important. Catalysts such as zinc chloride can be used in the reaction if necessary.



The rate of this reaction is dependent upon the nature of the hydrohalogen acid and upon the type of alcohol. The order of reactivity for the acids is  $\text{HI} > \text{HBr} > \text{HCl}$ . Tertiary alcohols are the most reactive, primary, the least. This difference in the reactivity of the three classes of alcohols provides a method for distinguishing them called the Lucas test. The reagent is a mixture of zinc chloride and concentrated hydrochloric acid. Since alkyl chlorides are not soluble in water, but alcohols of fewer than six carbons are, the production of an insoluble phase (alkyl halide) constitutes a positive test. At room temperature tertiary alcohols yield the chloride almost instantaneously, secondary alcohols do so in five minutes, but primary alcohols do not react.

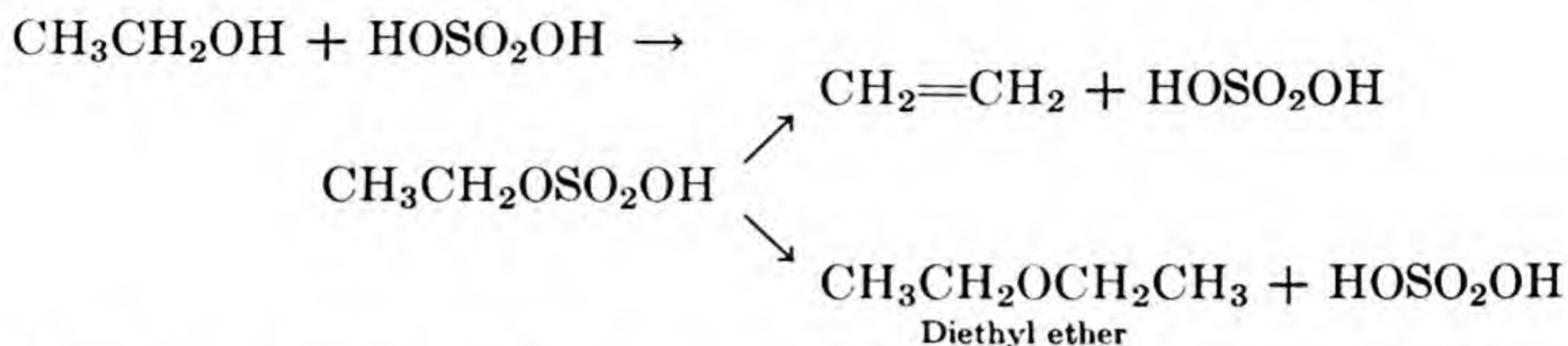
For the purpose of preparing alkyl halides from alcohols, phosphorus halides (or mixtures of phosphorus and the halogens) are often used. Thionyl chloride ( $\text{SOCl}_2$ ) is also frequently employed for the preparation of chlorides.



The reaction of alcohols with concentrated sulfuric acid yields the alkylsulfuric acids. Heating the reaction mixture causes further

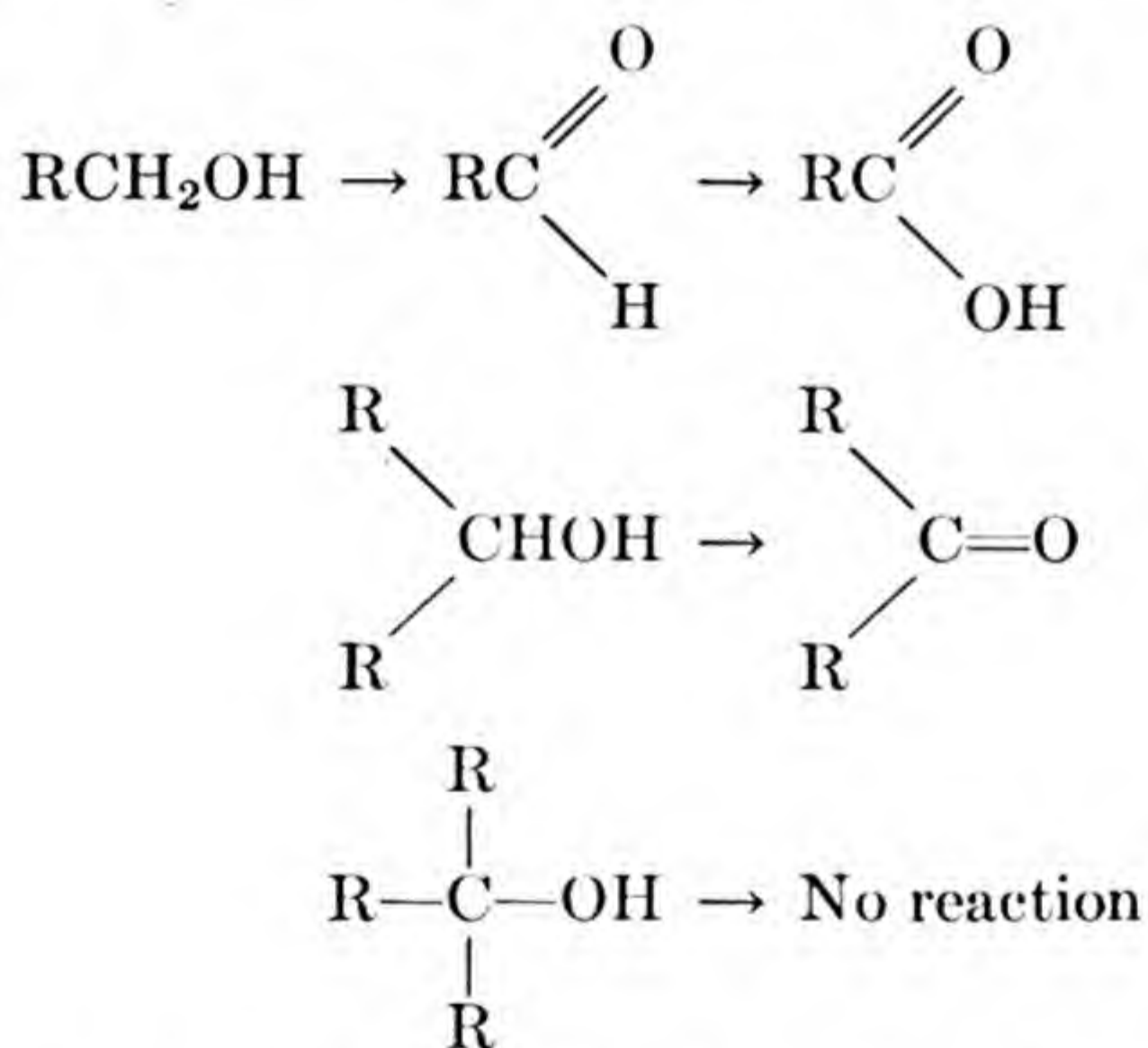


change, and the reaction may take two courses. With ethyl alcohol, for example, the changes may be represented as follows.



Both reactions are *dehydrations*; that is, the over-all effect of the sulfuric acid is the removal of one molecule of water from one or two molecules of the alcohol. In general, formation of the olefin is favored by higher temperatures. The type of alcohol has an effect also; tertiary alcohols undergo olefin formation most readily, and primary, least readily. In fact, most tertiary alcohols cannot be made to form ethers by this process.

The three types of alcohols behave differently when treated with oxidizing agents. Primary alcohols undergo a two-step oxidation in which an aldehyde is produced first, then an acid; both have the same carbon skeleton as the alcohol. Secondary alcohols yield ke-



tones which are not readily oxidized further. Tertiary alcohols do not undergo oxidation easily, and when they do the carbon chain is broken so that smaller molecules are obtained. The most frequently used oxidizing agent for these reactions is chromic acid,  $\text{H}_2\text{CrO}_4$ . It will be observed that the conversion of a primary alcohol to an aldehyde and a secondary alcohol to a ketone are in reality *dehydrogenations*; that is, the effect of the chromic acid is the removal of two hydrogen atoms which are oxidized to water.



## ► USES OF ALCOHOLS

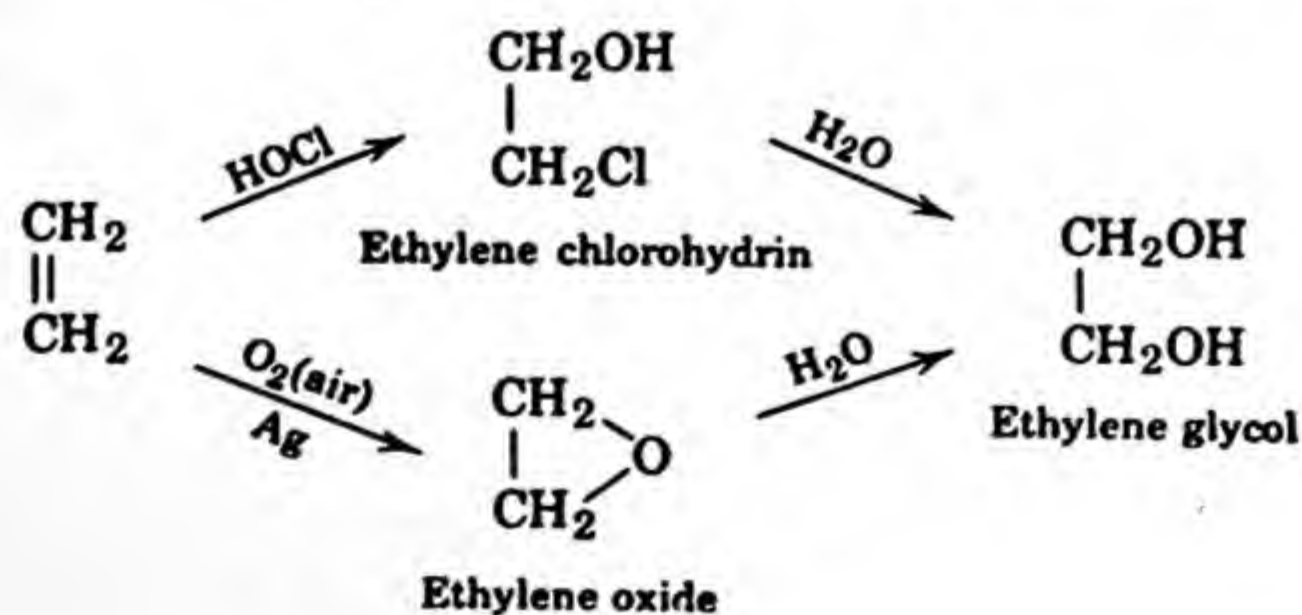
The lower alcohols, particularly methyl, ethyl, and isopropyl, are important solvents and are widely used in the finishes and plastics industries. All three are important raw materials in the preparation of other commercial products. Alcoholic beverages contain ethyl alcohol in various dilutions together with flavoring materials. In distilled liquors the concentration is expressed in "proof" numbers. This figure divided by 2 gives the percentage of alcohol by volume. Thus a whiskey which is 100 proof contains 50% alcohol by volume. At the present time the federal tax on beverage alcohol is more than twenty dollars per gallon of 95% alcohol. Alcohol used industrially is not so taxed, but in order to prevent its use as a beverage it is "denatured"; that is, substances are added to it which render it unfit to drink. Numerous denaturing formulas are used, depending upon the application of the alcohol.

A considerable amount of ethyl alcohol is employed as a solvent in the pharmaceutical industry. Many drugs are insoluble in water but soluble in ethanol, so that liquid prescriptions often contain alcohol to promote homogeneity.

Methyl and ethyl alcohols are used in antifreeze mixtures in automobile radiators. Because of their low boiling points they are considered to be the nonpermanent type.

As previously mentioned, primary alcohols can be oxidized to aldehydes or acids, and secondary alcohols, to ketones. Many of these oxidation products, such as formaldehyde and formic acid from methanol, acetaldehyde and acetic acid from ethyl alcohol, and acetone from isopropyl alcohol, are important industrial materials. Their applications are considered in Chapters 9 and 10.

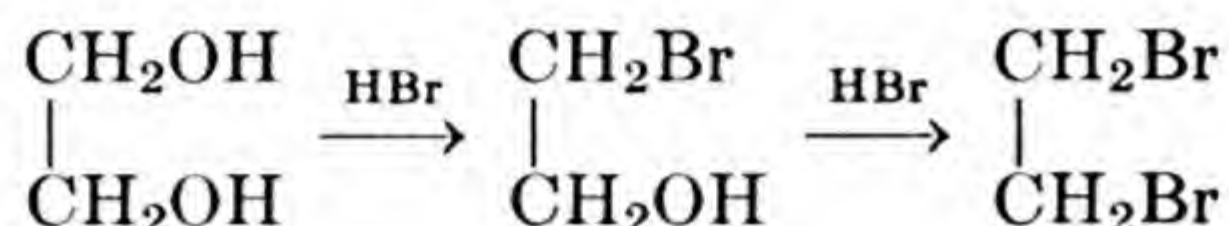
**Ethylene glycol.** Compounds having two hydroxyl groups are said to be diols or glycols. The most important of these is ethylene glycol, obtained from ethylene by several processes.



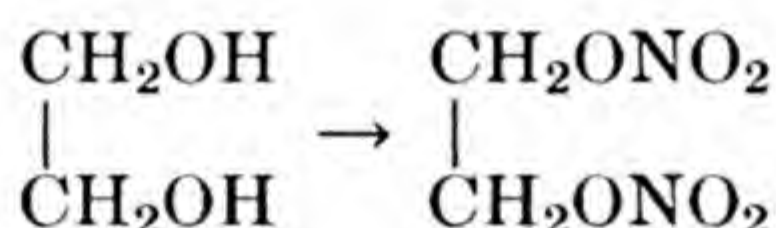


It is a viscous, colorless liquid, miscible with water in all proportions. Its high boiling point and slight solvent action on rubber and lacquers make it an excellent antifreeze. Though more expensive than methanol or ethanol, it is longer lasting.

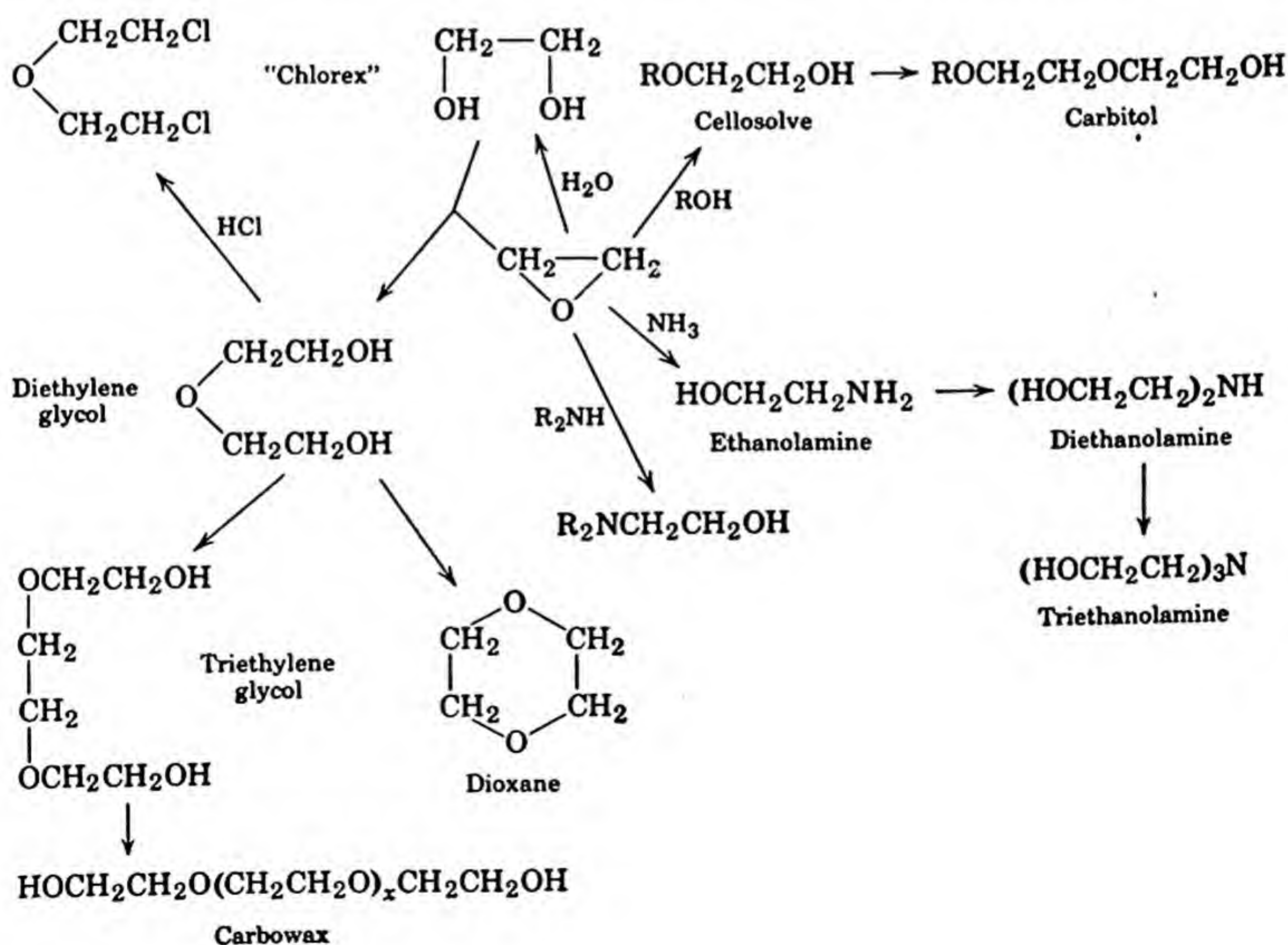
Ethylene glycol and other diols have reactions similar to those of the ordinary alcohols, but since they have two hydroxyl groups derivatives are known in which one or both of the functional groups have been transformed.



Ethylene glycol reacts with nitric and sulfuric acids to yield the dinitrate, a useful explosive.



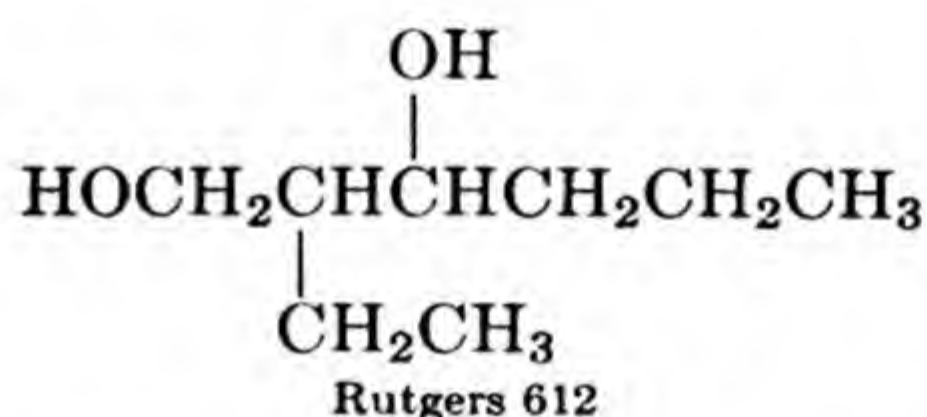
Ethylene oxide, a very reactive substance, is widely used for the introduction of the hydroxyethyl group ( $-\text{CH}_2\text{CH}_2\text{OH}$ ). The diagram below shows some of the commercial products made from ethylene oxide. It will be observed that in every case the oxide ring



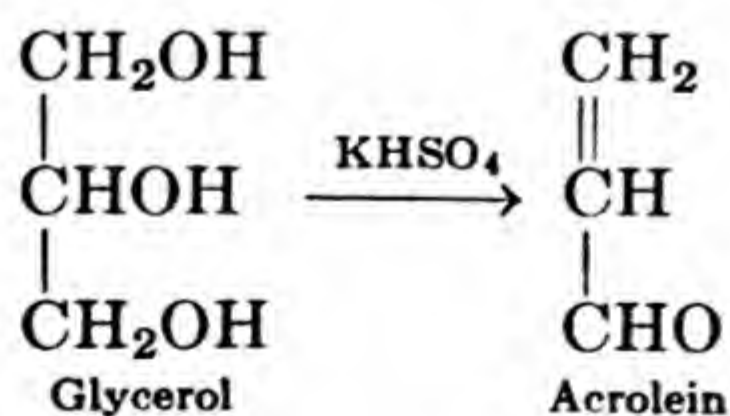


is cleaved and that hydrogen attaches to the oxygen atom; the rest of the reacting molecule attaches to the carbon atom. Water thus reacts with ethylene oxide to give ethylene glycol, which in turn can react with more ethylene oxide to give di-, tri-, and higher ethylene glycols. Di-, tri-, and tetraethylene glycols are oily liquids soluble in water. They are useful as humectants, *i.e.*, substances which have the property of attracting and retaining moisture, and are also employed to dry air and other gases. Carbowax, a polyethylene glycol, has a waxy feel and appearance and is a component of water-soluble wax preparations. Chlorex is used as a solvent in petroleum refining. Dioxane, the cellosolves, and the carbitols are all good solvents for organic compounds and are soluble in water. This fact makes it possible to obtain aqueous solutions of otherwise insoluble compounds. Ammonia and primary and secondary amines (Chapter 14) also react with ethylene glycol to give amino alcohols, which are valuable in the manufacture of some synthetic detergents and pharmaceuticals.

Another diol of interest is 2-ethyl-1,3-hexanediol (Rutgers 612), which has the power to repel insects. It is especially effective with mosquitoes and, since it is odorless, is widely employed by sportsmen and those whose work is out-of-doors.

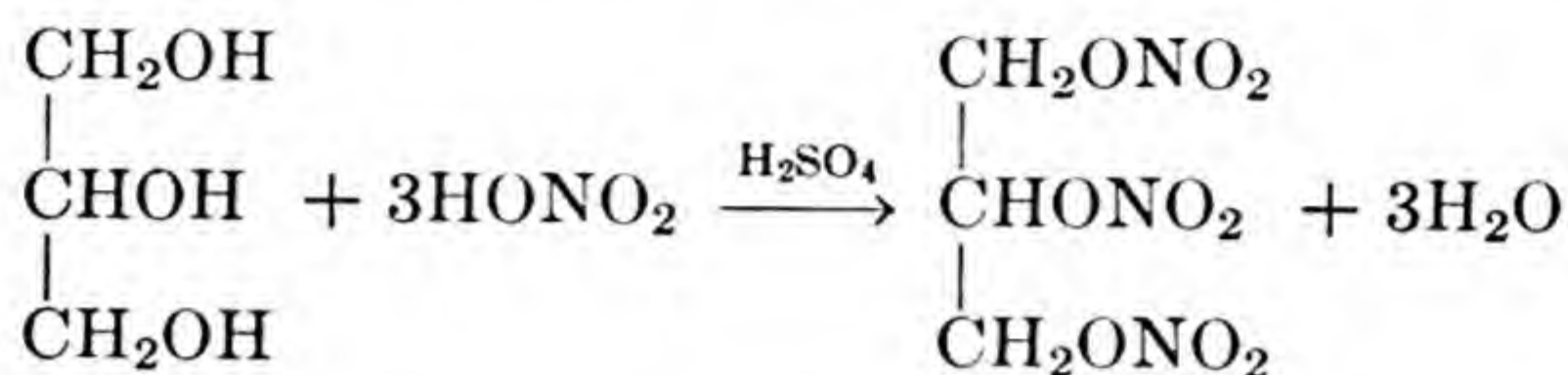


**Glycerol.** When a fat or vegetable oil is heated with aqueous sodium hydroxide, a soap and glycerol are produced. Though the soap industry provides the most important source of glycerol, it is also obtained in controlled fermentations of sugar and by a synthetic process from propylene. Glycerol has three hydroxyl groups, two primary and one secondary, and it therefore forms several series of derivatives. It loses water upon heating, especially with a dehydrating agent, to give acrolein, an unsaturated aldehyde.

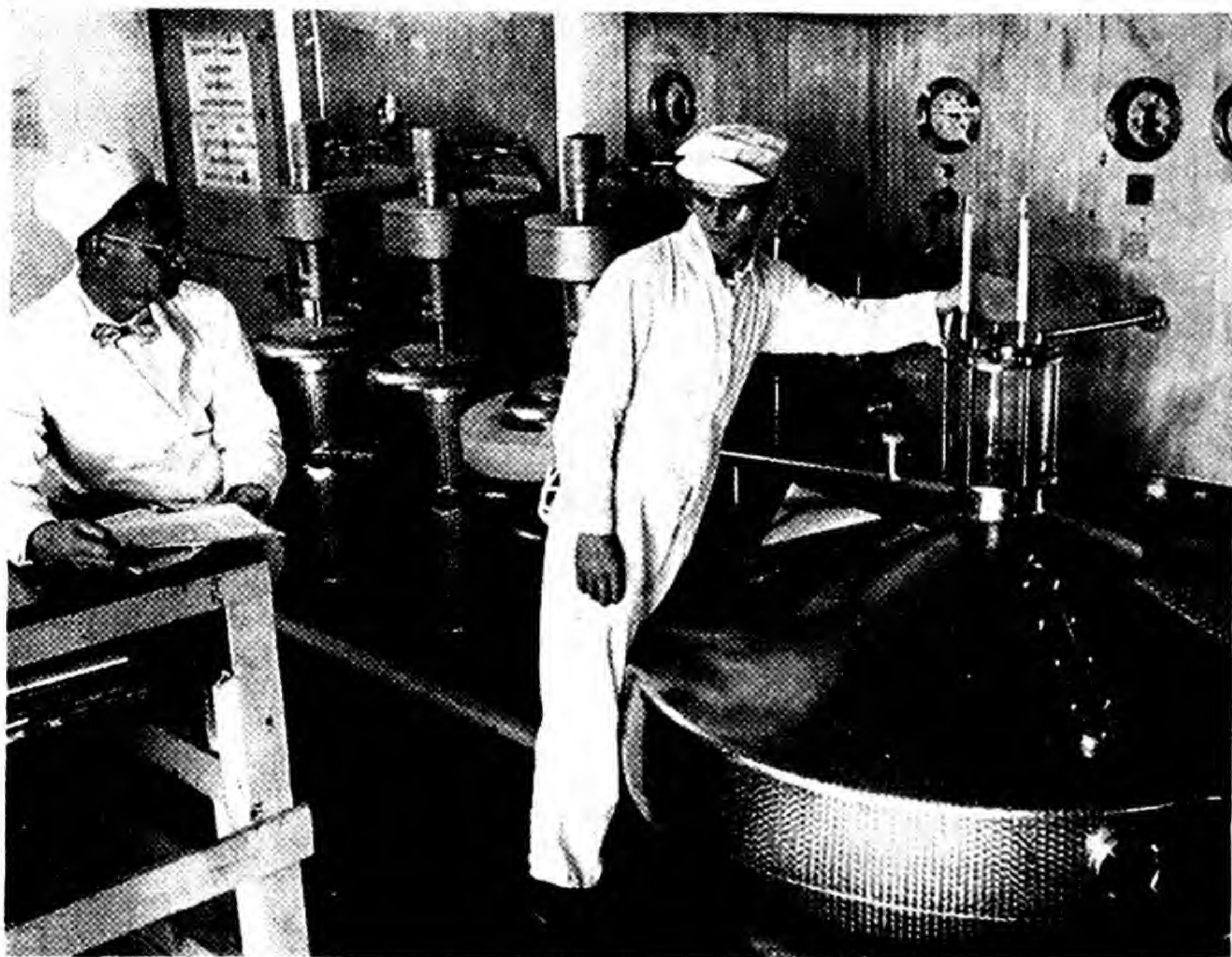




The sharp irritating odor of burning fat is due to acrolein. If glycerol is treated with a mixture of nitric and sulfuric acids, the important explosive, glyceryl trinitrate (nitroglycerin), is obtained. It is a yellowish, very unstable liquid, and great care must be taken



in its preparation and handling. Because of its sensitivity nitroglycerin is usually absorbed in an inert material, such as clay or sawdust. The product, dynamite, is much less sensitive.



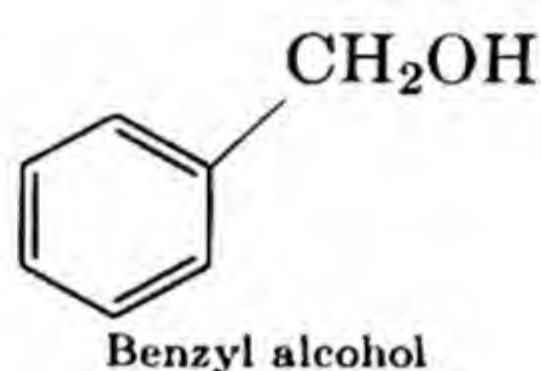
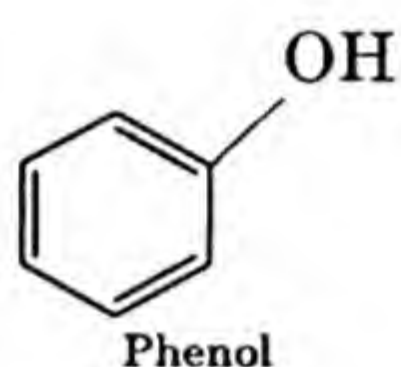
Apparatus used in the manufacture of nitroglycerin. The equipment shown employs the continuous Biazzi process, an additional safety feature of which is that the nitroglycerin concentration is kept at a much lower figure than that customary in the batch process. Such extreme care is exercised in explosive plants that the accident rate is superior to that in many other industries usually considered safer. (Photograph courtesy of the Du Pont Company.)



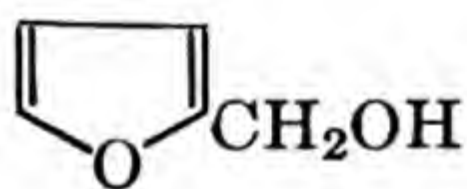
Glycerol is an oily liquid with a sweet taste. It is hygroscopic, completely miscible with water, and boils at 290°. Large amounts of glycerol are used for humectant purposes. Ink pads, stencils, and smoking tobacco contain glycerol to help keep them moist. It is used in large quantities in cellophane as a plasticizer to impart flexibility and toughness to the product. Glycerol is employed in the manufacture of synthetic resins used in finishes. It is added to alcoholic beverages and candies as a blending agent.

### ► AROMATIC ALCOHOLS

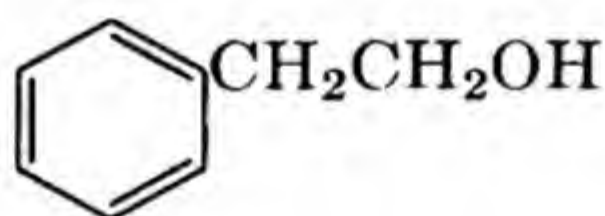
A hydroxyl group joined to an aromatic ring has weakly acidic properties. Such compounds are called phenols and are not classed



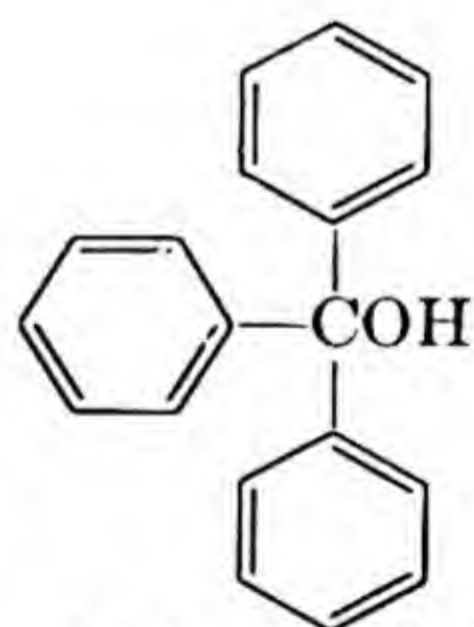
as alcohols. In aromatic alcohols an aromatic ring and a hydroxyl group are present, but they are not linked together. The hydroxyl group in such compounds is much like that in the aliphatic alcohols. Benzyl alcohol is the simplest aromatic alcohol; other well-known examples are the following.



Furfuryl alcohol



2-Phenylethanol



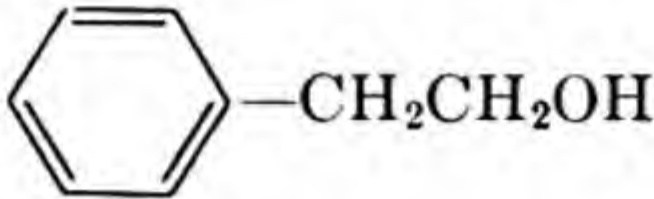
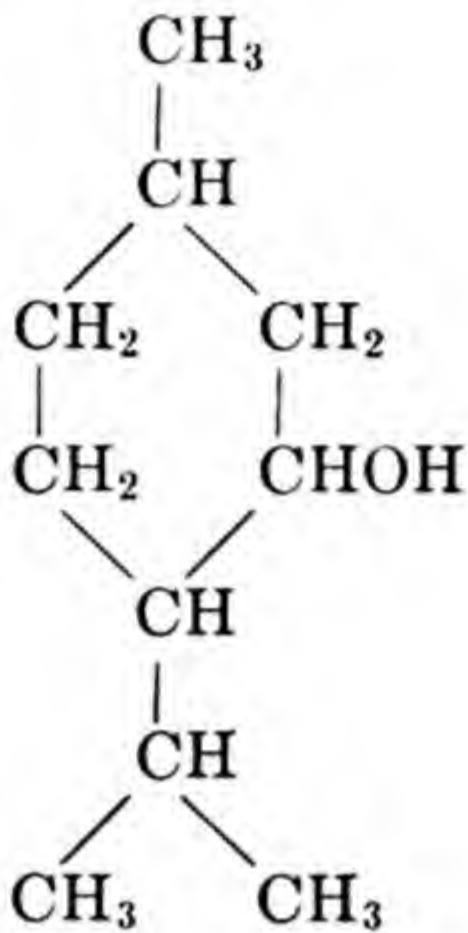
Triphenylmethanol

### ► ALCOHOLS THAT OCCUR IN NATURE

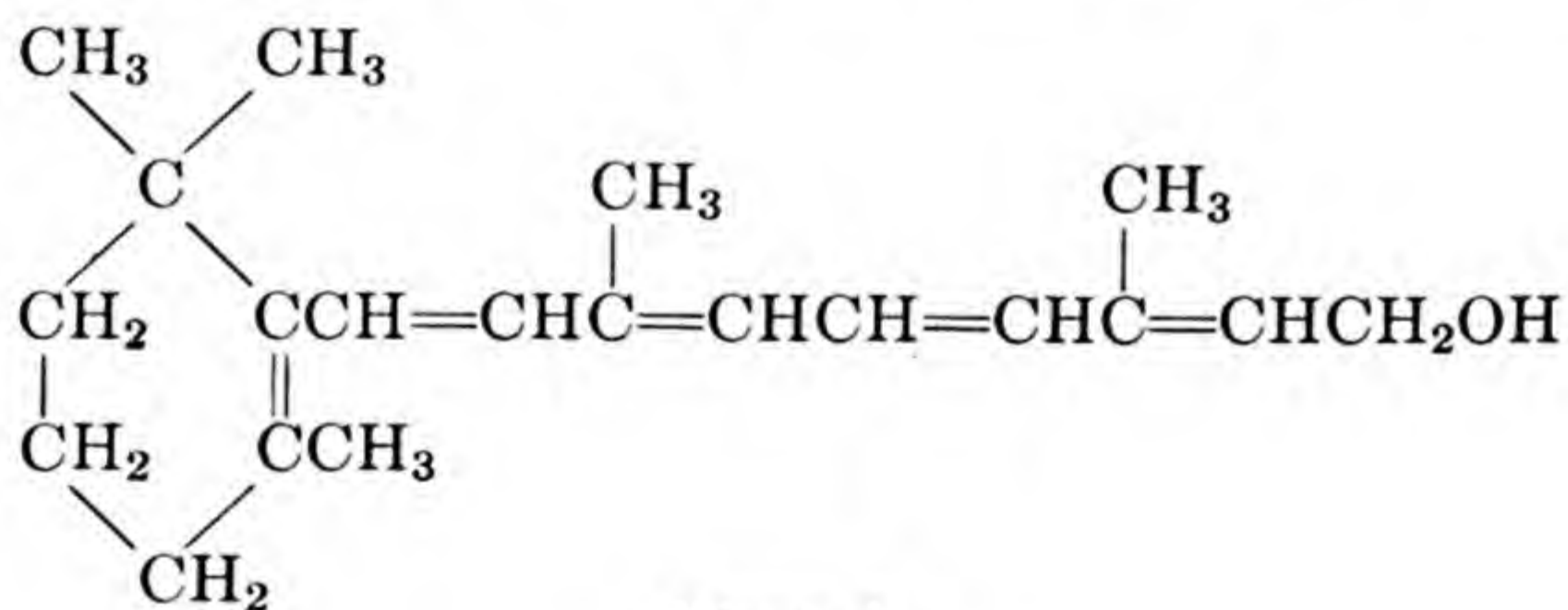
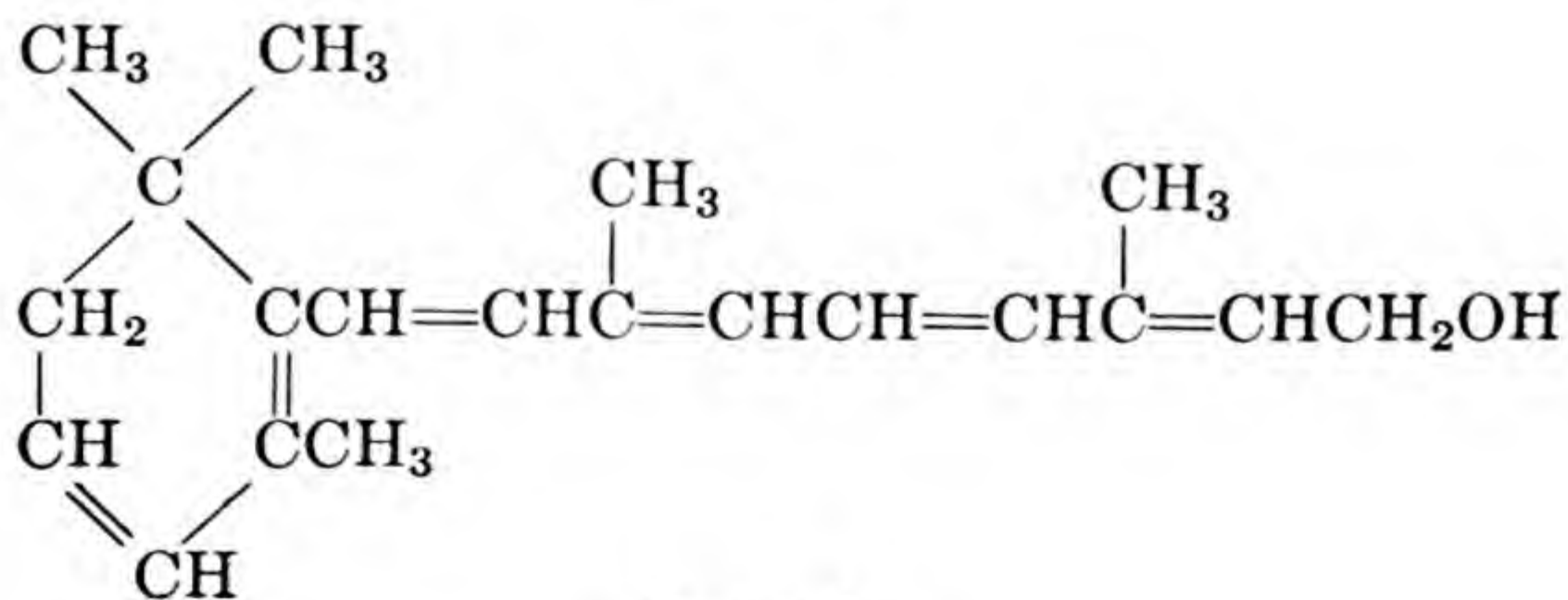
Numerous alcohols are found in nature. They are produced by plants and are often responsible for the characteristic odors in certain species. Some examples are given in the following table.



## Some Naturally Occurring Alcohols

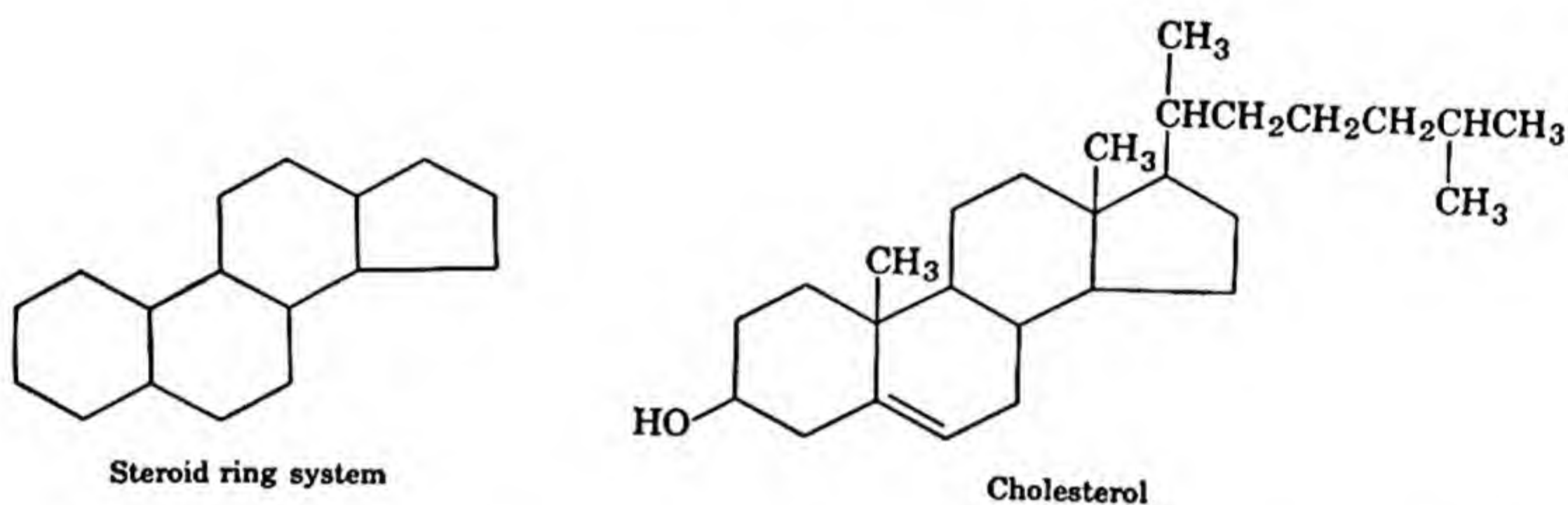
Name	Structure	Occurrence
3-Hexen-1-ol	$\text{CH}_3\text{CH}_2\text{CH}=\text{CHCH}_2\text{CH}_2\text{OH}$	Tea
2,6-Nonadien-1-ol	$\text{CH}_3\text{CH}_2\text{CH}=\text{CHCH}_2\text{CH}_2\text{CH}=\text{CHCH}_2\text{OH}$	Violet
2-Phenylethanol		Rose, geranium
Menthol		Peppermint
Geraniol	$\text{CH}_3-\underset{\text{CH}_3}{\text{C}}=\text{CHCH}_2\text{CH}_2\underset{\text{CH}_3}{\text{C}}=\text{CHCH}_2\text{OH}$	Geranium

The vitamins A are alcohols of physiological importance.

Vitamin A<sub>1</sub>Vitamin A<sub>2</sub>

Both  $A_1$  and  $A_2$  are highly unsaturated. It is interesting that their unsaturation is conjugated and that their carbon skeleton obeys the isoprene rule. The commonest symptom of vitamin A deficiency in man is night blindness, in which the eyes adapt poorly to changes in light intensity. Good sources of this vitamin are butter, milk, eggs, liver, and especially fish-liver oils. It is interesting that vitamin  $A_2$  occurs in the livers of fresh-water fish, and  $A_1$ , in the livers of ocean fish. A number of carotenoids (Chapter 5) can be converted into vitamin  $A_1$  by the body. They are found in fresh vegetables, such as lettuce and carrots.

**Sterols.** The sterols are alcohols of complex structure that occur in plants and animals. They are tetracyclic and possess the ring system sketched, which occurs very widely in nature.

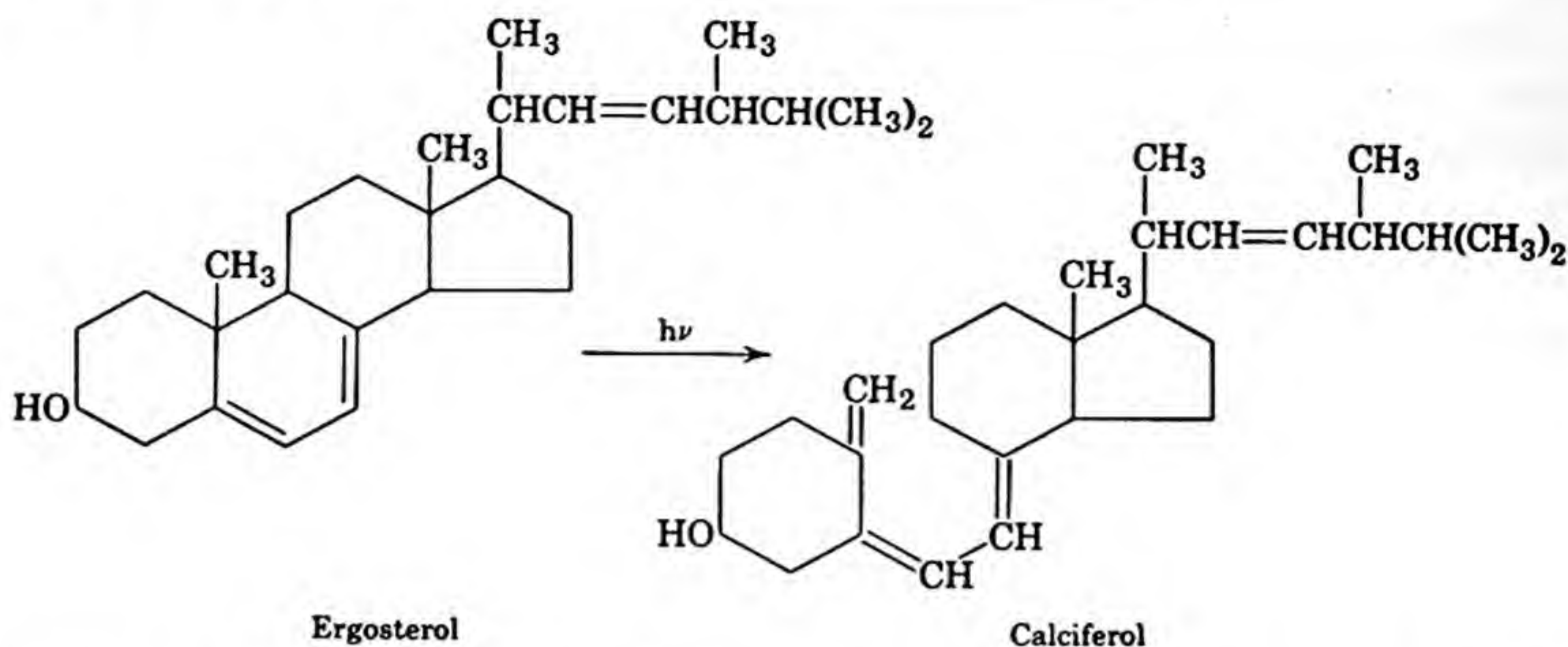


Cholesterol, whose structure is also shown, occurs in all cells of animal organisms but in the largest amounts in the brain, nervous tissue, and adrenal cortex. The solid matter of the human brain contains about 17% cholesterol, and some gallstones, nearly 100%. It appears that the body uses cholesterol as a raw material to synthesize the adrenal cortex hormones. Abnormally high levels of cholesterol in the blood apparently lead to some forms of cardio-vascular disease.

Ergosterol is a plant sterol, irradiation of which yields calciferol (vitamin  $D_2$ ). It is not definitely known whether this conversion takes place in man, though it has been suggested that the ergosterol of the skin is converted to calciferol through the agency of sunlight, a process which occurs in lower animals.

The mechanism of the biochemical activity of vitamin D is unknown, but it plays a part in growth and especially in bone formation and maintenance. Insufficient D in the diet of children leads to rickets, the symptoms of which are bowed legs and soft and brittle bones. With adults, insufficient D leads to easily broken and porous





bones. It should be noted that rickets can also result from insufficient calcium or phosphorus in the diet or an insufficiency of the hormone of the parathyroid.

## ► QUESTIONS

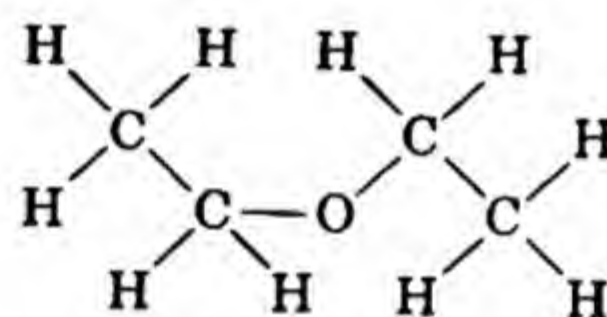
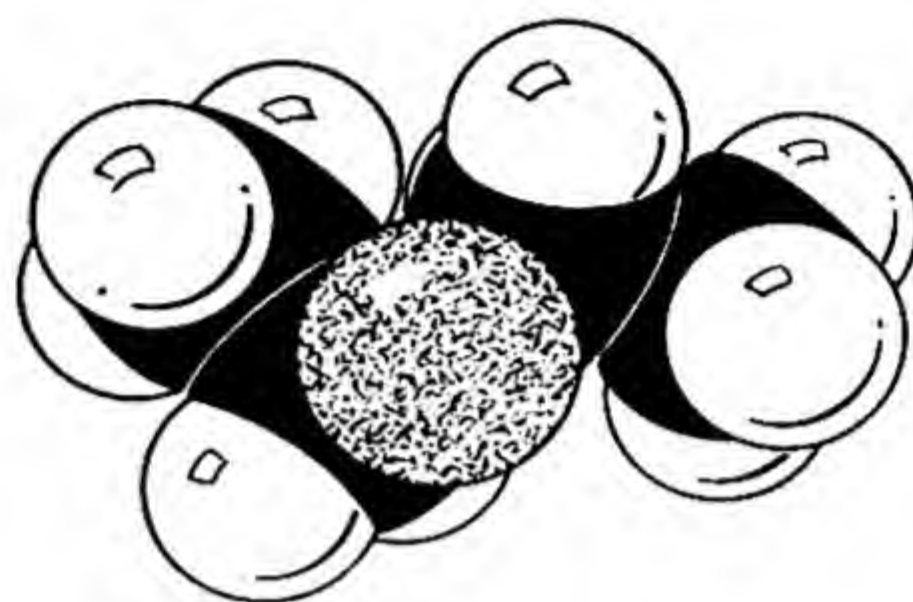
1. Write the formulas for the following alcohols and classify them as primary, secondary, or tertiary:

- (a) 2-Methyl-2-butanol
- (b) 2,2-Diphenyl-1-propanol
- (c) *p*-Chlorobenzyl alcohol
- (d) 3-Pentanol

2. Show the structures of the products formed in the following reactions:

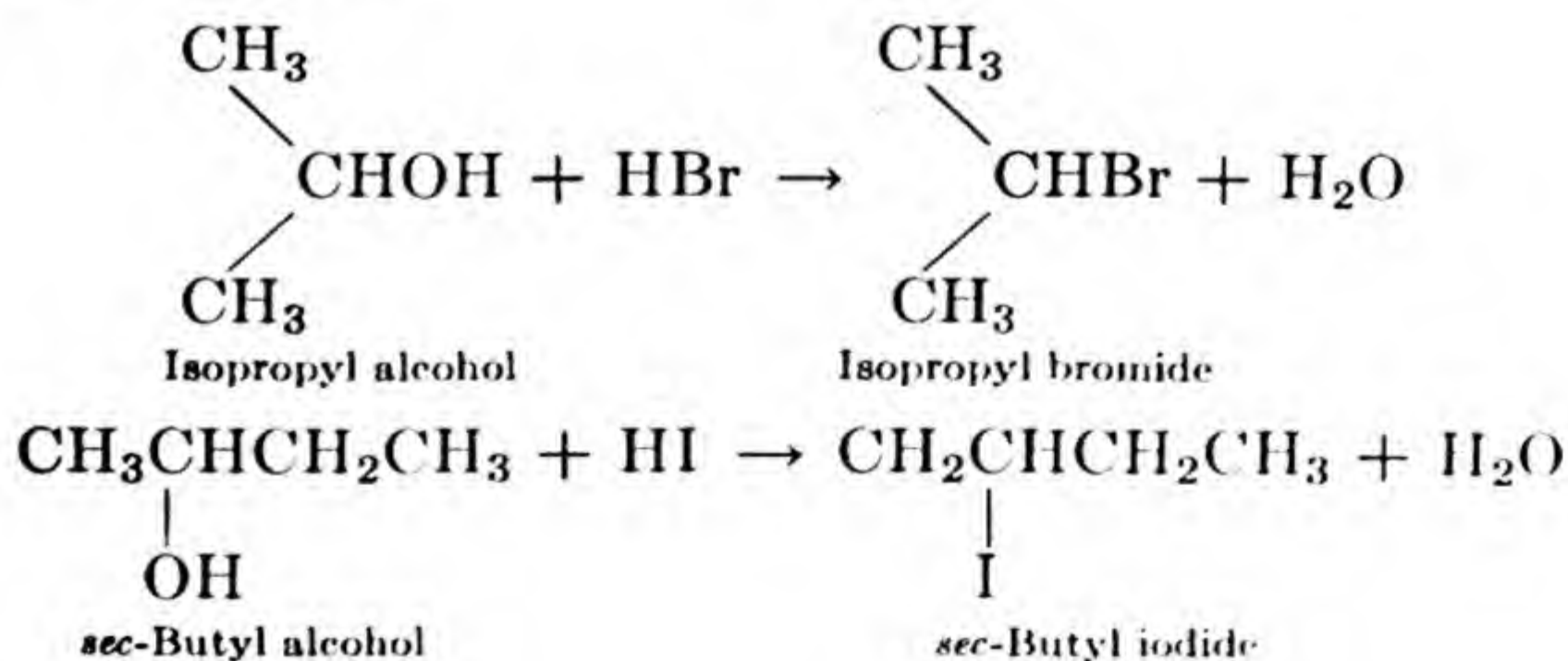
- (a) Cyclohexanol +  $\text{H}_2\text{CrO}_4 \rightarrow$
- (b) 2-Methyl-3-pentanol +  $\text{HCl} \xrightarrow{\text{ZnCl}_2}$
- (c) Ethylene glycol +  $\text{H}_2\text{SO}_4 \rightarrow$
- (d) 1-Pentanol + sodium  $\rightarrow$

3. Write the structural formulas for all alcohols having the molecular formula  $\text{C}_5\text{H}_{12}\text{O}$ . Give legitimate names for them and classify them as primary, secondary, or tertiary.



## ► ALKYL HALIDES

The alkyl halides may be represented by the general formula  $C_nH_{2n+1}X$ , or  $RX$ . The usual procedure for obtaining these compounds consists in the reaction of an alcohol with a hydrohalogen acid or a phosphorus halide. Their common names are derived from those of the alcohols.



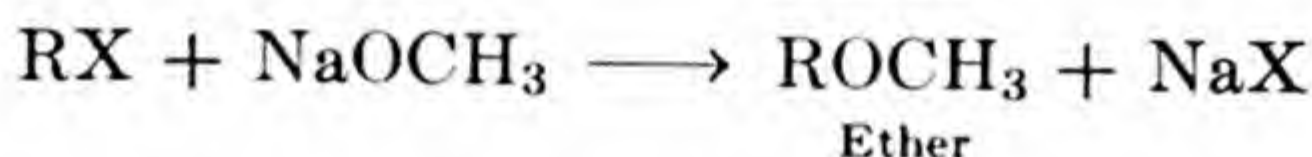
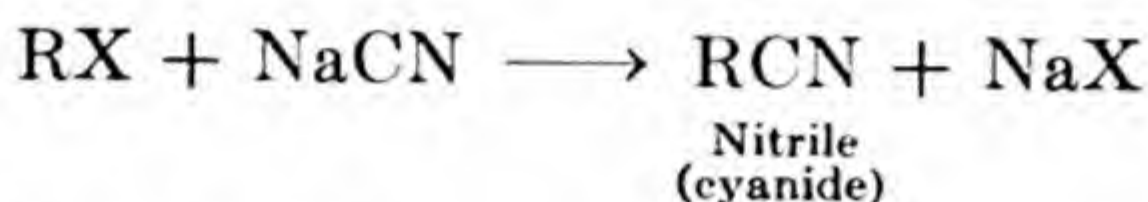
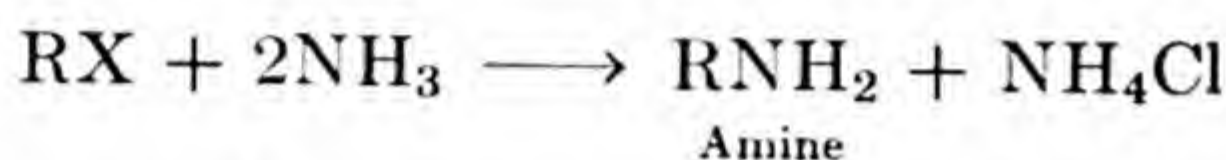
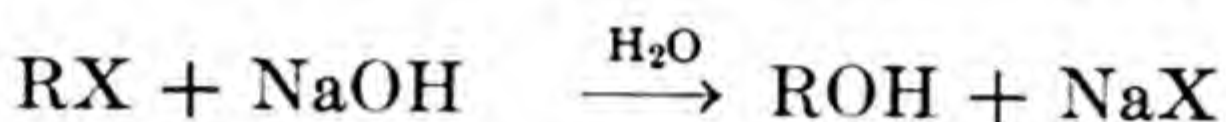


Another preparative method used occasionally consists in the addition of a hydrohalogen acid to an olefin.

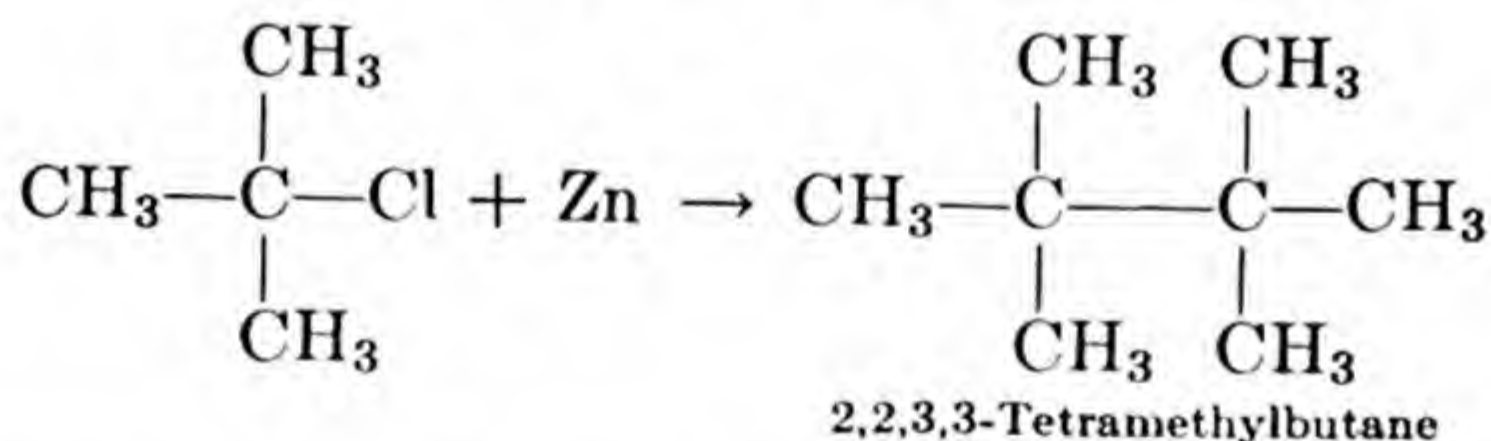
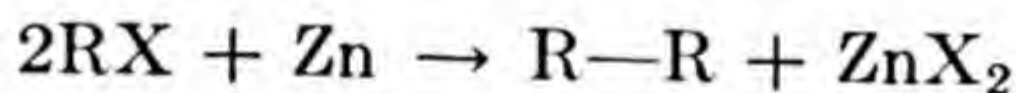


The applicability of this reaction is limited by the operation of Markovnikoff's rule (p. 32). For example, *n*-butyl halides cannot be prepared in this way.

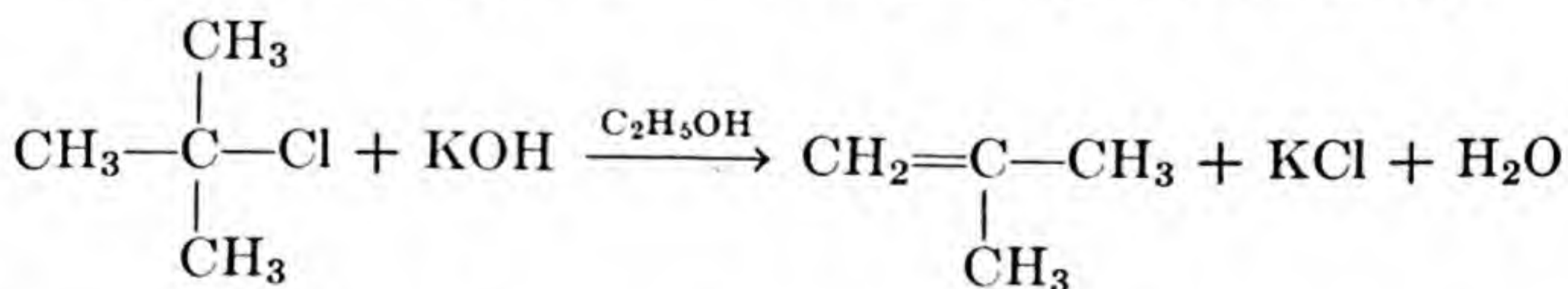
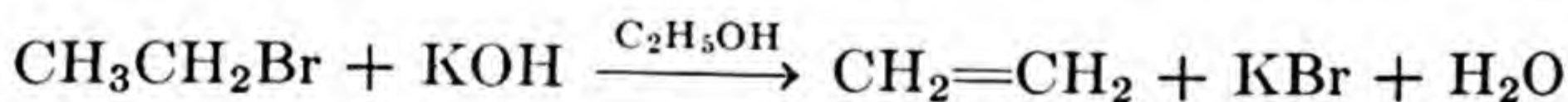
Because of their reactivity and versatility the alkyl halides are useful synthetic reagents. The halogen atom is the seat of reactivity, and it can be replaced by many other groups.



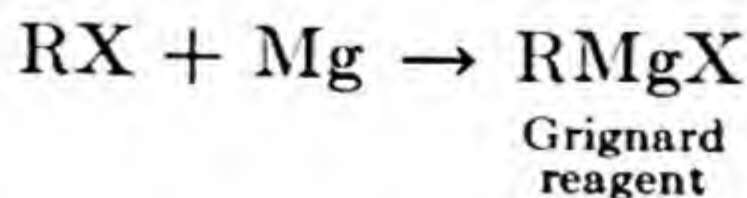
The Wurtz reaction, which consists in heating an alkyl halide with a metal such as zinc or sodium, provides a method of synthesis of paraffins.



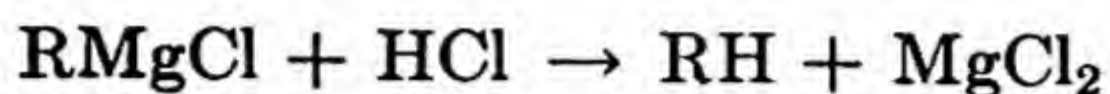
Olefins can be made by heating the halides with a solution of a base.



The alkyl halides undergo an important reaction with metallic magnesium in the presence of an ether.



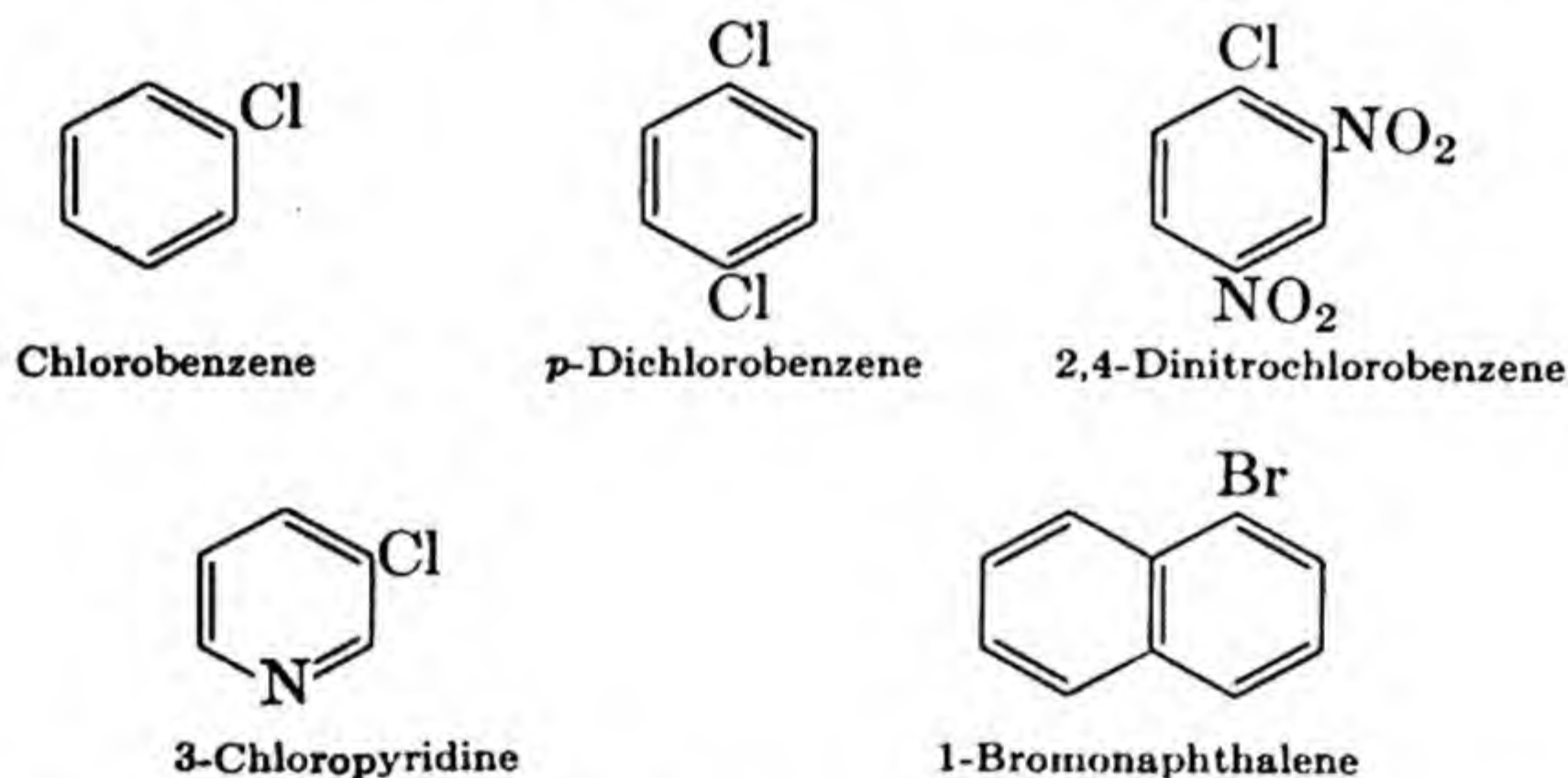
The products are known as alkylmagnesium halides or Grignard reagents and are very useful synthetic tools. For example, treatment with water or dilute acid yields hydrocarbons.



Various other applications of the Grignard reagent are encountered in discussions of other classes of compounds.

## ► ARYL HALIDES

Compounds having a halogen atom attached directly to an aromatic ring are said to be aryl halides. They are prepared either by direct halogenation (p. 44) or from aromatic primary amines (Chapter 14). Halogen derivatives in which the halogen atom is connected to a side chain are not considered aryl halides because their chemistry is like that of the alkyl halides. Some typical aryl halides are



The replacement of the halogen atoms by other groups, which occurs easily with alkyl halides, is difficult under ordinary conditions with aryl halides. High temperatures and pressures are usually needed. Aryl bromides do, for the most part, readily form Grignard reagents which can be employed in synthesis in much the same way as alkylmagnesium halides.

## ► ETHERS

The ethers may be represented generally by the formula  $\text{ROR}'$  in which the groups joined to the oxygen may be aliphatic or aromatic. If  $\text{R}$  and  $\text{R}'$  are identical, the ether is said to be a simple, or sym-



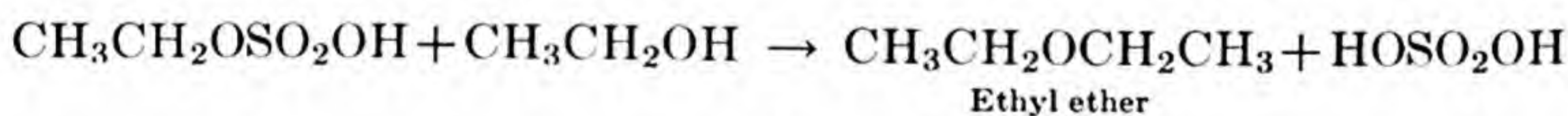
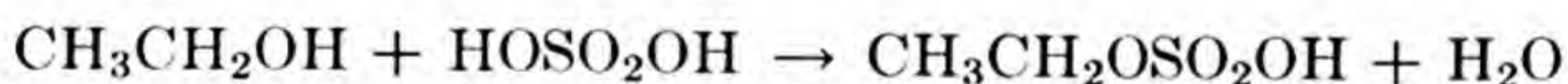
metrical, ether; if R and R' are different, the ether is said to be mixed, or unsymmetrical.

### Ethers

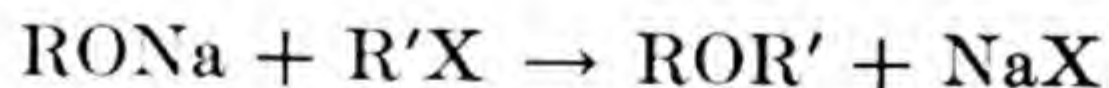
Name	Formula	Boiling Point	Class
Methyl ether	$\text{CH}_3\text{OCH}_3$	$-24^\circ$	Aliphatic
Ethyl methyl ether	$\text{CH}_3\text{OCH}_2\text{CH}_3$	$+10$	Aliphatic, mixed
Ethyl ether	$\text{C}_2\text{H}_5\text{OC}_2\text{H}_5$	35	Aliphatic
<i>n</i> -Butyl ether	$n\text{-C}_4\text{H}_9\text{OC}_4\text{H}_9\text{-}n$	142	Aliphatic
Anisole	$\text{C}_6\text{H}_5\text{OCH}_3$	155	Aromatic-aliphatic
Phenyl ether	$\text{C}_6\text{H}_5\text{OC}_6\text{H}_5$	259	Aromatic
Phenyl <i>p</i> -tolyl ether	$\text{C}_6\text{H}_5\text{O}-\text{C}_6\text{H}_4-\text{CH}_3$	278	Aromatic, mixed

The aliphatic ethers are named by enumerating the groups attached to the oxygen and following with the word "ether." When only one group is named it is understood that the ether is symmetrical. When the word "ether" is used alone ethyl ether is meant. Aromatic ethers often have trivial names.

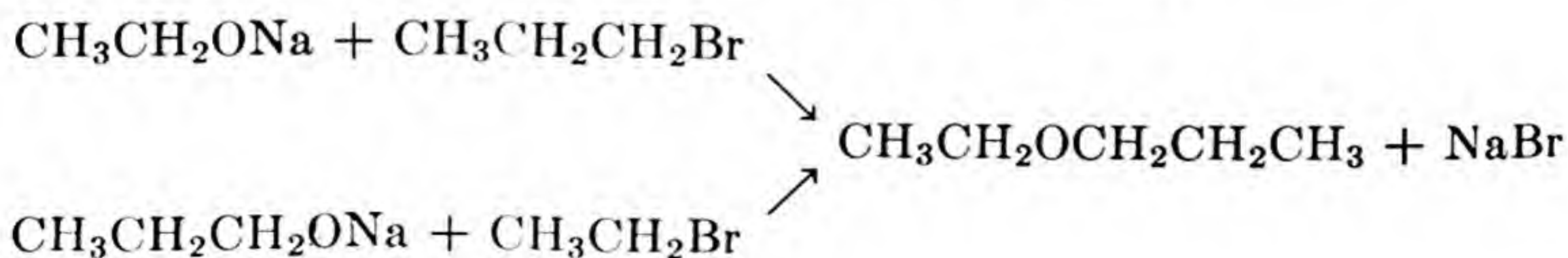
Symmetrical aliphatic ethers are usually made from the proper alcohols by treating the latter with a dehydrating agent such as sulfuric acid (see Chapter 7). With ethyl alcohol and sulfuric acid, the optimum temperature is  $140\text{--}150^\circ$ . Above  $150^\circ$  decomposition of the intermediate ethylsulfuric acid to ethylene becomes the predominant reaction.



Mixed ethers are best prepared by the Williamson synthesis, which involves the reaction of an alkyl halide and a sodium alkoxide.

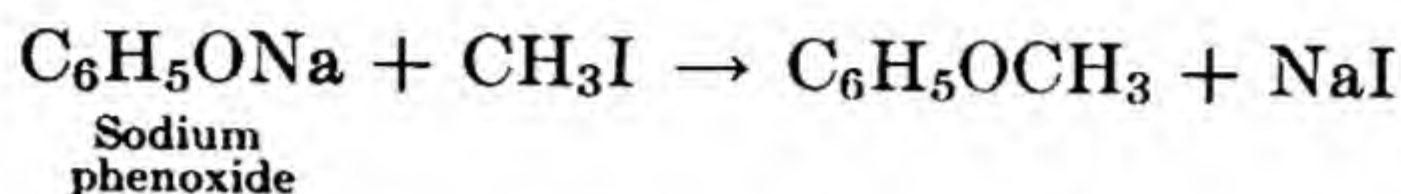


For mixed aliphatic ethers two routes are theoretically possible. An illustration is the preparation of ethyl *n*-propyl ether.

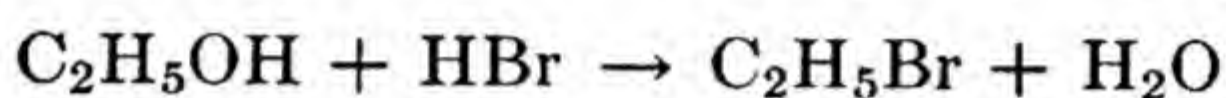
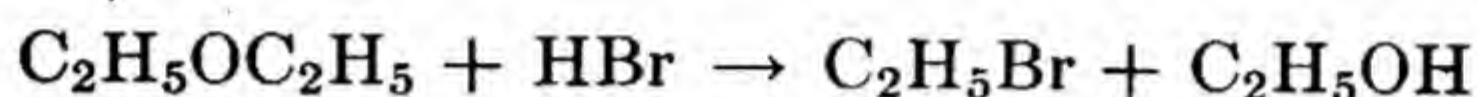




The Williamson synthesis is particularly suitable for the preparation of alkyl aryl ethers such as anisole. Since the phenols are acidic, it is customary to use a solution of the phenol in aqueous sodium hydroxide instead of isolating the phenoxide.



The ethers are relatively unreactive. They can, however, be cleaved by the action of hot, concentrated hydrobromic or hydriodic acid. Ethyl ether, for example, reacts to give ethyl bromide. The reaction takes place in two steps:

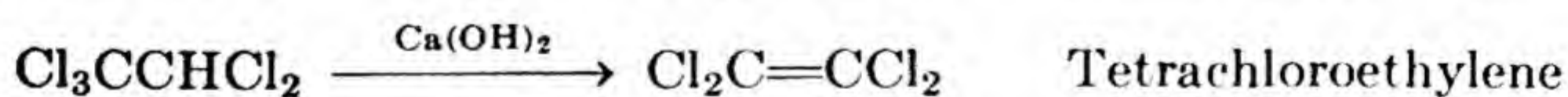
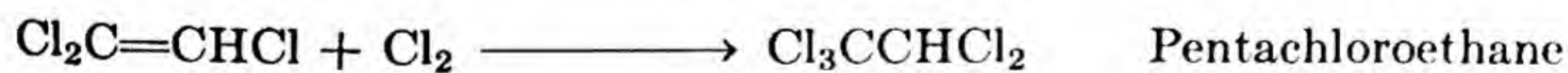
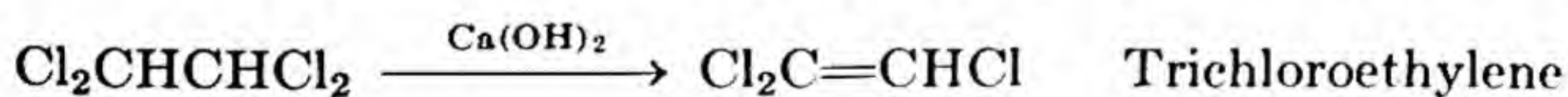
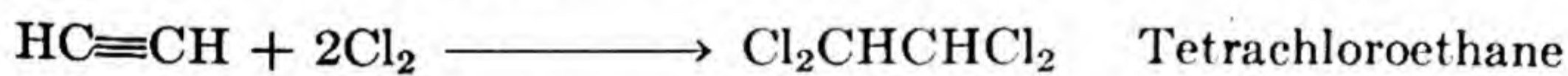


Upon standing in contact with air the ethers are slowly oxidized to peroxides, which are explosive substances. Since the peroxides are higher boiling than the ethers, the evaporation of the ether concentrates the peroxide and increases the danger.

Because of their inertness ethers are used chiefly as solvents. Ethyl ether is widely employed as a general anesthetic. The discovery of this property of ethyl ether was an important step in the development of modern surgery.

## ► APPLICATIONS OF HALOGEN DERIVATIVES

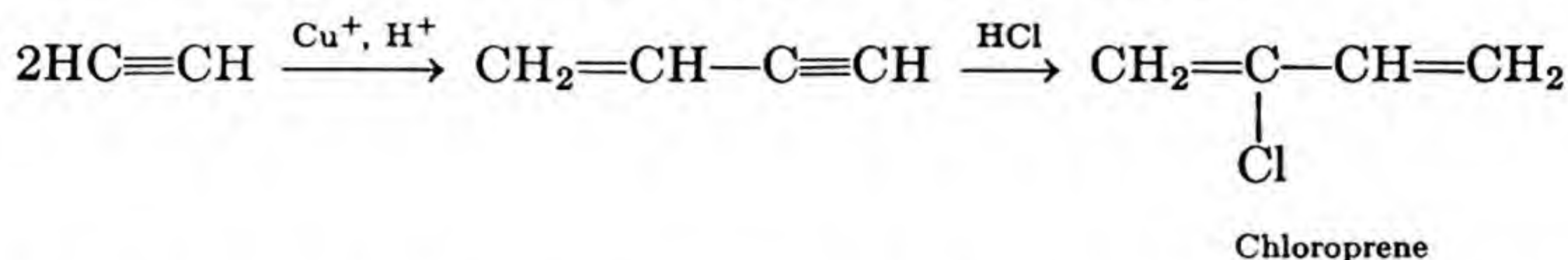
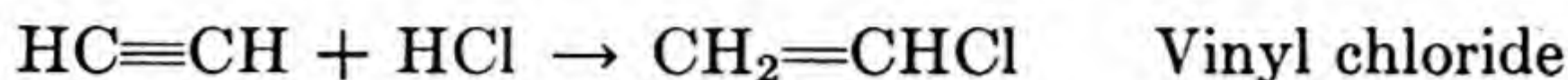
The halogen derivatives of the hydrocarbons have good solvent power for organic compounds, a property which permits their employment as dry-cleaning solvents and as metal-degreasing agents. Two such solvents, tetrachloroethylene and trichloroethylene, which are of special value in the dry-cleaning operation, are made from acetylene. Tetrachloroethane is employed as a metal degreaser.



Acetylene is also employed in the preparation of certain halogen compounds which are raw materials in the plastics industry. Of

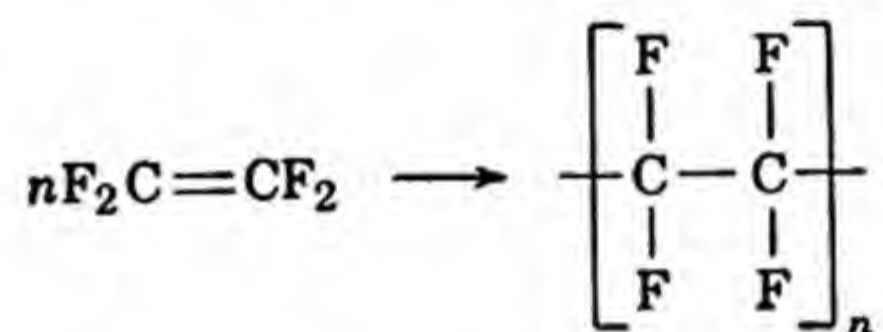


these, vinyl chloride and chloroprene are the most important:



It will be recalled that chloroprene is polymerized to yield neoprene (Chapter 5), a synthetic rubber.

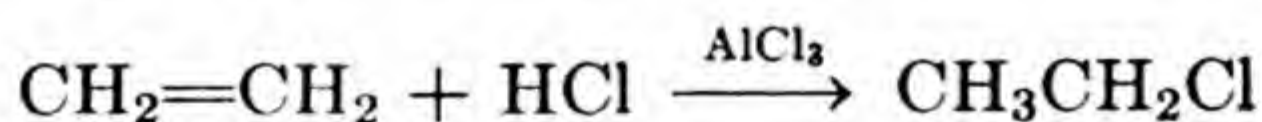
Of the halogen-containing synthetic polymers, the most remarkable is polytetrafluoroethylene (Teflon). It is not attacked by any organic solvent or by concentrated sulfuric acid or fuming nitric acid. It



will withstand temperatures of 400 to 500° F and has excellent insulating properties. Because of its refractory nature it is difficult to shape, and it is expensive. It is employed in specialty applications, such as gaskets in equipment handling corrosive material or operating at a high temperature, and for electrical insulation in which light weight is important.

Polychlorotrifluoroethylene is more workable than polytetrafluoroethylene, but its chemical resistance, though superior to that of all other plastics, is inferior to that of polytetrafluoroethylene.

Ethyl chloride, an industrially important compound, is prepared by the reaction of ethyl alcohol with hydrogen chloride and by the addition of hydrogen chloride to ethylene. It is used principally in the manufacture of tetraethyllead, which is added to nearly all gasolines to improve their octane rating. The reactants are ethyl chloride and sodium-lead alloy. Ethyl fluid also contains ethylene chloride and ethylene bromide.

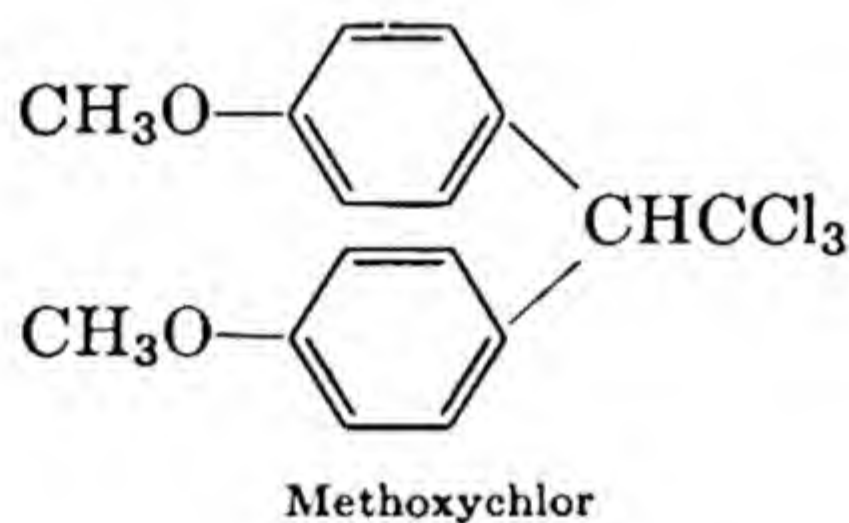
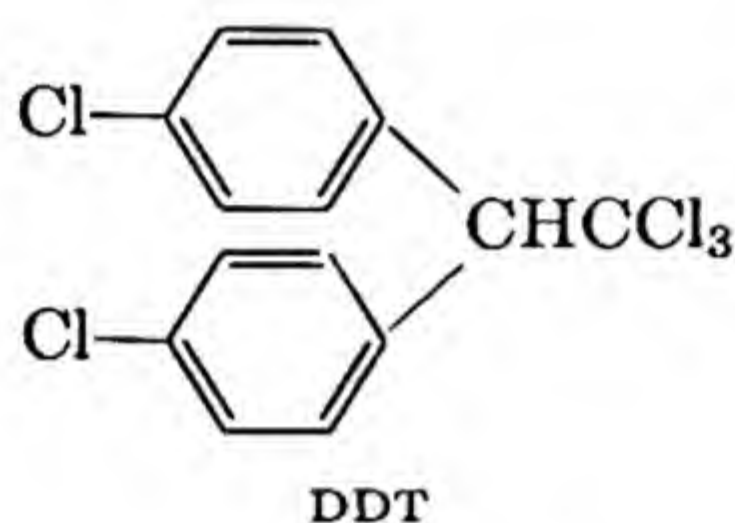


If tetraethyllead alone is added to gasolines, lead oxide deposits appear in the engine, especially in the valves. The ethylene halides

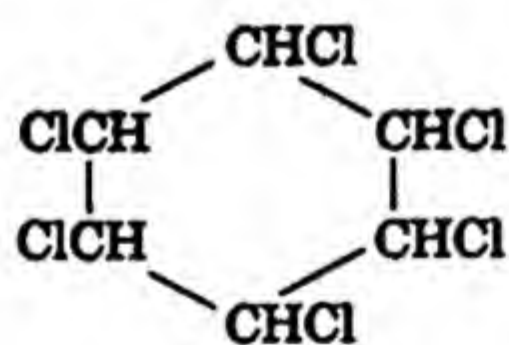


circumvent this by converting the lead into volatile lead compounds which are expelled in the exhaust gases. Ethylene chloride and bromide are made by the addition of the appropriate halogen to ethylene. Ethyl chloride is also employed as a surface anesthetic in minor surgery, such as the removal of warts.

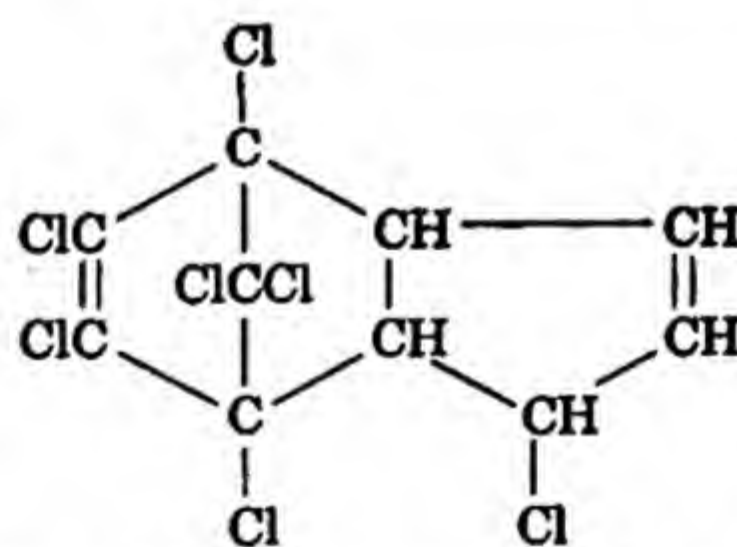
A number of chlorine compounds have come into prominence as insecticides. The first of these to gain importance was DDT. Though it was first employed as a general insecticide, its application has gradually become more restricted because resistant strains of insects, particularly flies, have developed. Methoxychlor, a compound of similar structure, has had the same kind of history.



In addition to DDT and its relatives, other chlorine-containing compounds have been found to be effective insecticides. Lindane is one of the nine stereoisomers of 1,2,3,4,5,6-hexachlorocyclohexane. Stereoisomers differ only in the spatial distribution of the constituent atoms and groups (p. 123 and Chapter 12). Lindane is obtained by the addition of chlorine to benzene, along with a number of insecti-



1,2,3,4,5,6-Hexachlorocyclohexane

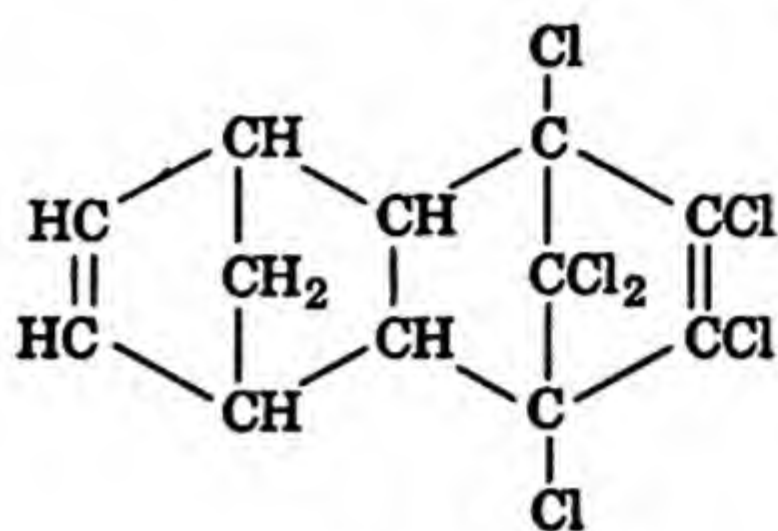


Heptachlor (a component of Chlordan)

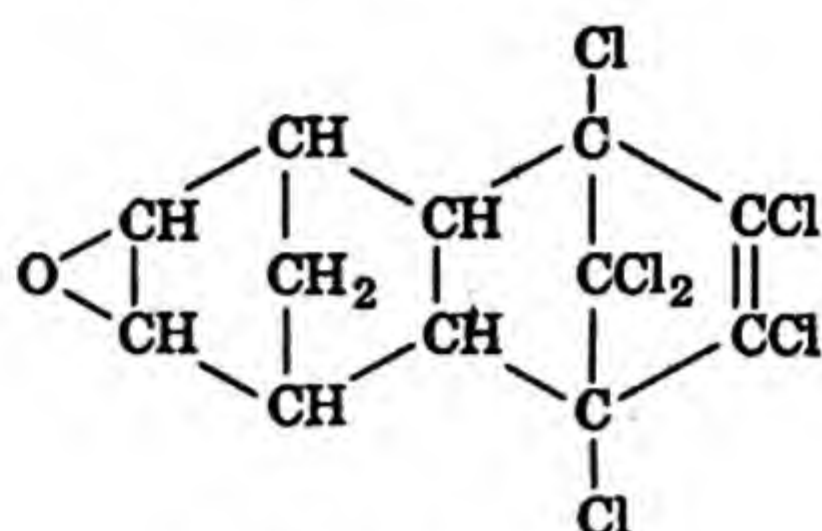
cidally inactive isomers. It is used in household and garden sprays. The mixture of isomers, often in company with DDT and sulfur, is applied to cotton. Chlordan, a mixture of chlorine compounds of similar structure, is widely used as a general insecticide and is especially harmful to roaches, ants, termites, and certain soil-dwelling insects. The similar compounds aldrin, dieldrin, and endrin (a stereoisomer of dieldrin) have been employed with success against cotton



pests. Toxaphene, a complex mixture obtained by chlorinating camphene, is also a valuable agricultural insecticide.



Aldrin



Dieldrin (Endrin)

## ► QUESTIONS \_\_\_\_\_

1. Show by equations what would occur if methyl ethyl ether were heated with concentrated hydriodic acid.

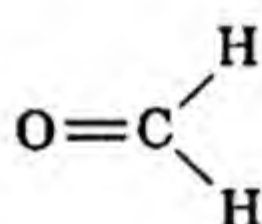
2. Show by equations how *n*-butyl bromide would react with the following reagents under appropriate conditions:

- (a) Aqueous sodium hydroxide
- (b) Alcoholic sodium hydroxide
- (c) Sodium ethoxide
- (d) Zinc
- (e) Ammonia
- (f) Sodium cyanide

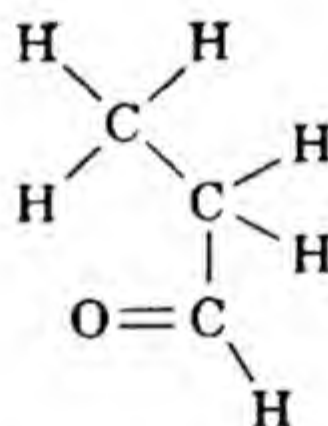
3. Write equations for the following syntheses:

- (a) Methyl *n*-propyl ether from methanol and 1-propanol
- (b) Hexane from *n*-propyl alcohol
- (c) Butane from *n*-butyl bromide
- (d) Isopropyl bromide from *n*-propyl bromide

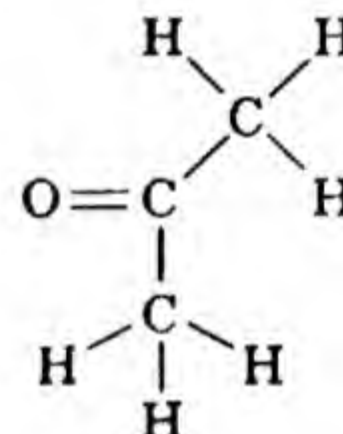
# Aldehydes and ketones



Formaldehyde



Propionaldehyde



Acetone

The aldehydes and ketones are among the most versatile of organic compounds. The carbonyl group ( $\text{—}\overset{\text{O}}{\underset{\parallel}{\text{C}}}\text{—}$ ), possessed by

both types of compound, is more exposed to attack in the aldehydes which are therefore more reactive.

## ► CARBONYL COMPOUNDS

Aldehydes and ketones contain the carbonyl group,  $\text{C}=\text{O}$ . If one or both of the bonds of the carbonyl group are attached to hydro-



gen atoms, the compound is said to be an aldehyde. The functional

group of aldehydes is  $\begin{array}{c} \text{H} \\ | \\ -\text{C} \\ || \\ \text{O} \end{array}$  (or  $-\text{CHO}$ ). In ketones both bonds of

the carbonyl group are attached to *carbon* atoms. The aldehydes

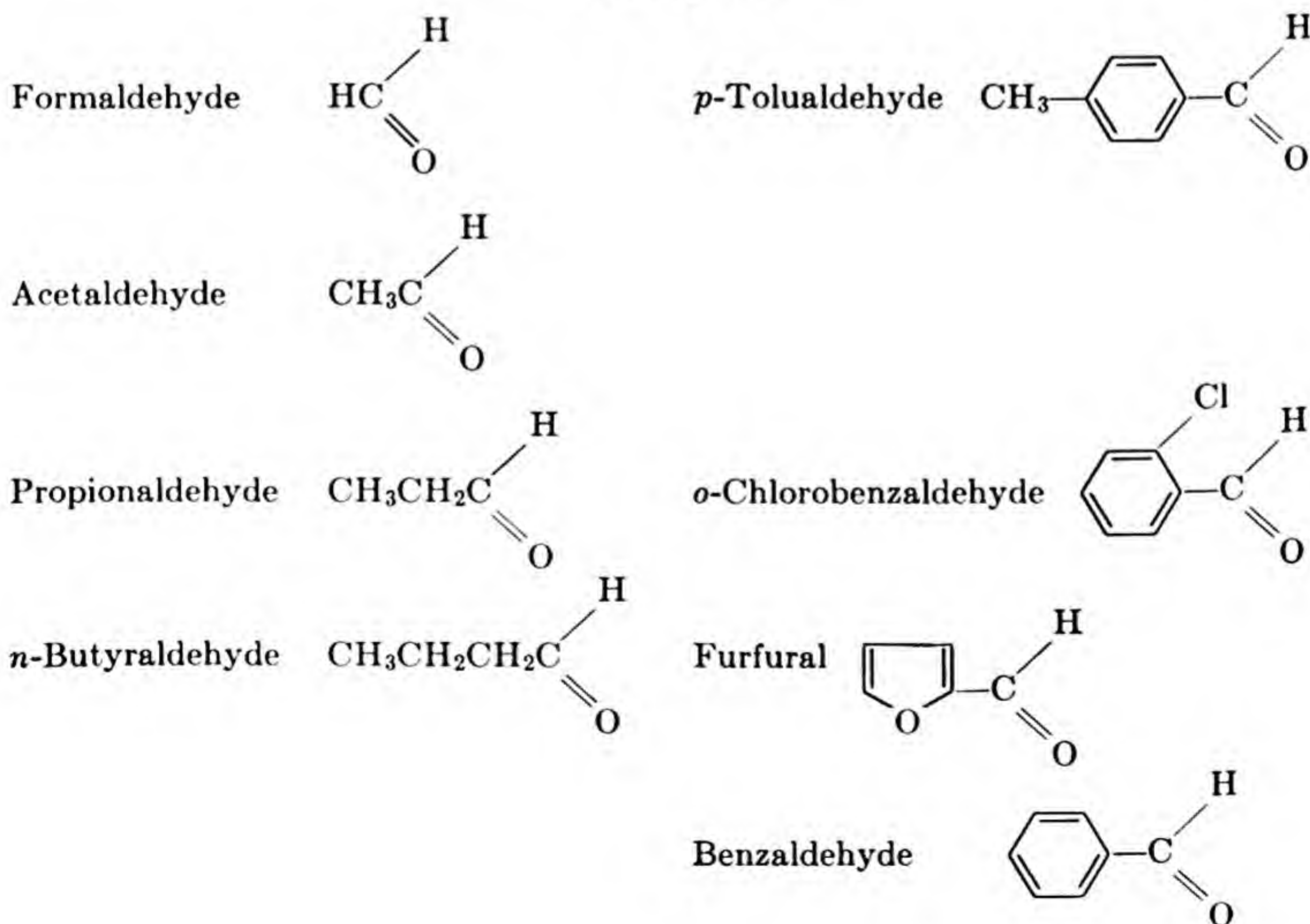
therefore can generally be represented as  $\text{RC} \begin{array}{c} \text{H} \\ | \\ || \\ \text{O} \end{array}$ , and the ketones,

$\begin{array}{c} \text{R} \\ | \\ \text{C}=\text{O} \\ | \\ \text{R}' \end{array}$ . Because both possess the carbonyl group the two series of

compounds have similar properties, and it is profitable to consider them simultaneously. Differences in behavior are noted at the appropriate places.

**Nomenclature of the Aldehydes.** It has been mentioned previously that aldehydes readily undergo oxidation to acids, and the

### Aldehydes



common names of the two are also related. Thus formaldehyde yields formic acid upon oxidation, and benzaldehyde furnishes benzoic acid. The common names and formulas for a few typical aldehydes are given in the table. The ending for the systematic names is -al, but systematic nomenclature is seldom used except with complex members of the series.

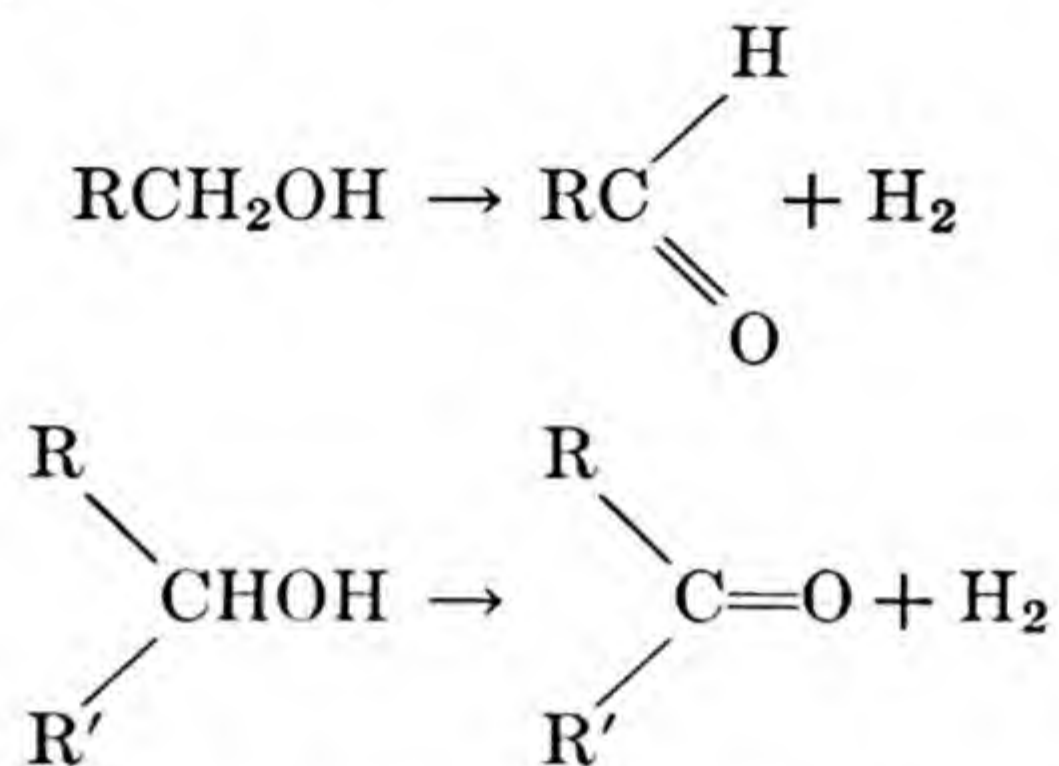
**Nomenclature of the Ketones.** Ketones are named according to several systems. For aliphatic ketones the common practice consists in enumerating the groups attached to the carbonyl group and following with the word "ketone." The "IUC" system of nomenclature uses the ending -one, which is treated in the same way as other suffixes. For ketones containing the benzene ring the "phenone" method is used. Here the ketones are considered to be derivatives of the acids. Inspection of the formulas and names in the table will give an insight into these methods.

Common Name	Ketones	
	IUC Name	Formula
Acetone	Propanone	$\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_3\text{CCH}_3 \end{array}$
Methyl ethyl ketone	Butanone	$\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_3\text{CCH}_2\text{CH}_3 \end{array}$
Diethyl ketone	3-Pentanone	$\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_3\text{CH}_2\text{CCH}_2\text{CH}_3 \end{array}$
Methyl isobutyl ketone	4-Methyl-2-pentanone	$\begin{array}{c} \text{O} \qquad \text{CH}_3 \\ \parallel \qquad   \\ \text{CH}_3\text{CCH}_2\text{CHCH}_3 \end{array}$
Acetophenone		$\begin{array}{c} \text{O} \\ \parallel \\ \text{C}_6\text{H}_5\text{CCH}_3 \end{array}$
Benzophenone		$\begin{array}{c} \text{O} \\ \parallel \\ \text{C}_6\text{H}_5\text{C}-\text{C}_6\text{H}_5 \end{array}$
<i>p</i> -Nitroacetophenone		$\begin{array}{c} \text{O} \\ \parallel \\ \text{O}_2\text{N}-\text{C}_6\text{H}_4\text{CCH}_3 \end{array}$
Cyclohexanone	Cyclohexanone	$\begin{array}{c} \text{CH}_2-\text{CH}_2 \\ \diagdown \quad \diagup \\ \text{CH}_2 \qquad \text{C=O} \\ \diagup \quad \diagdown \\ \text{CH}_2-\text{CH}_2 \end{array}$

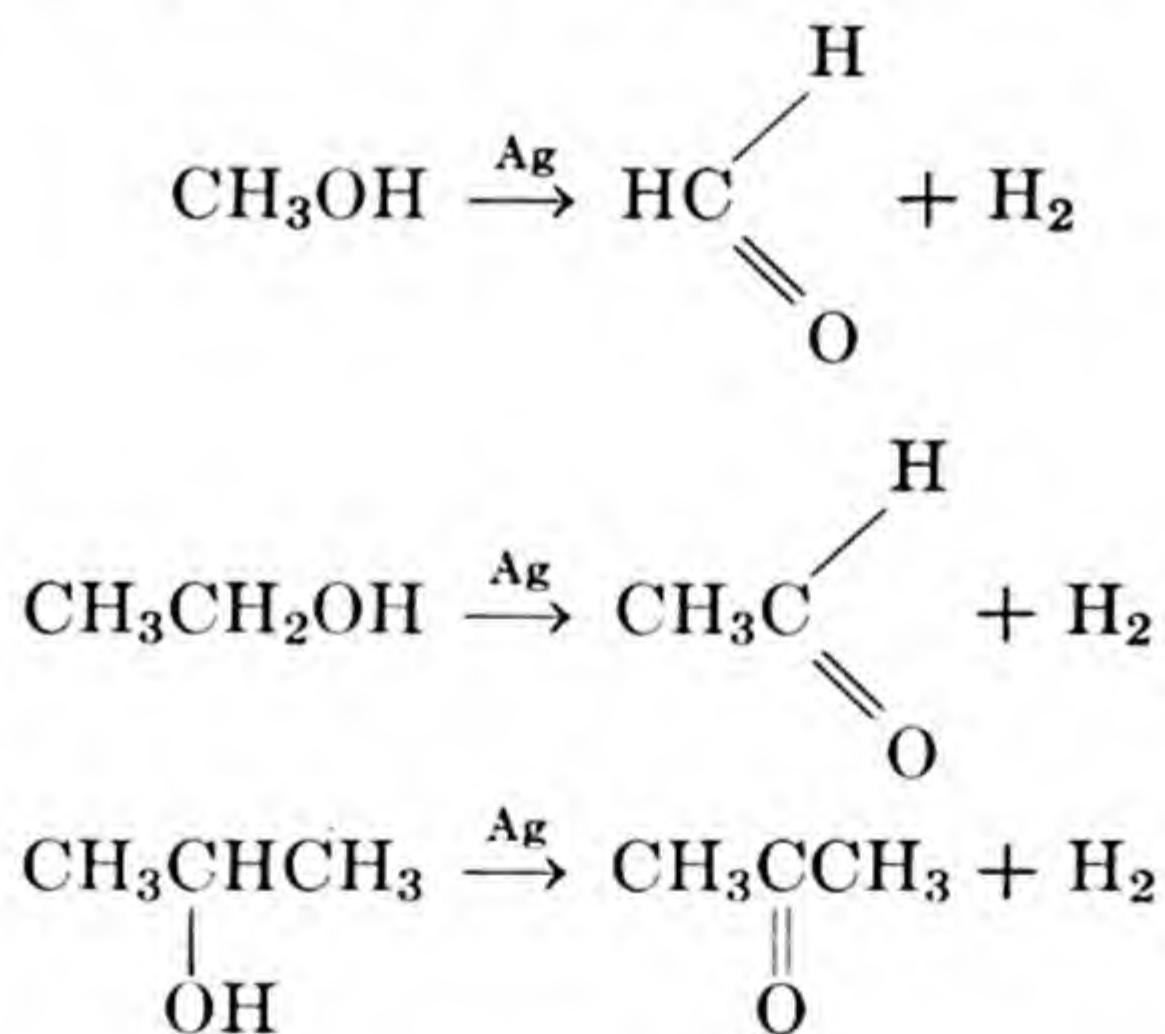


► **PREPARATION OF CARBONYL COMPOUNDS**

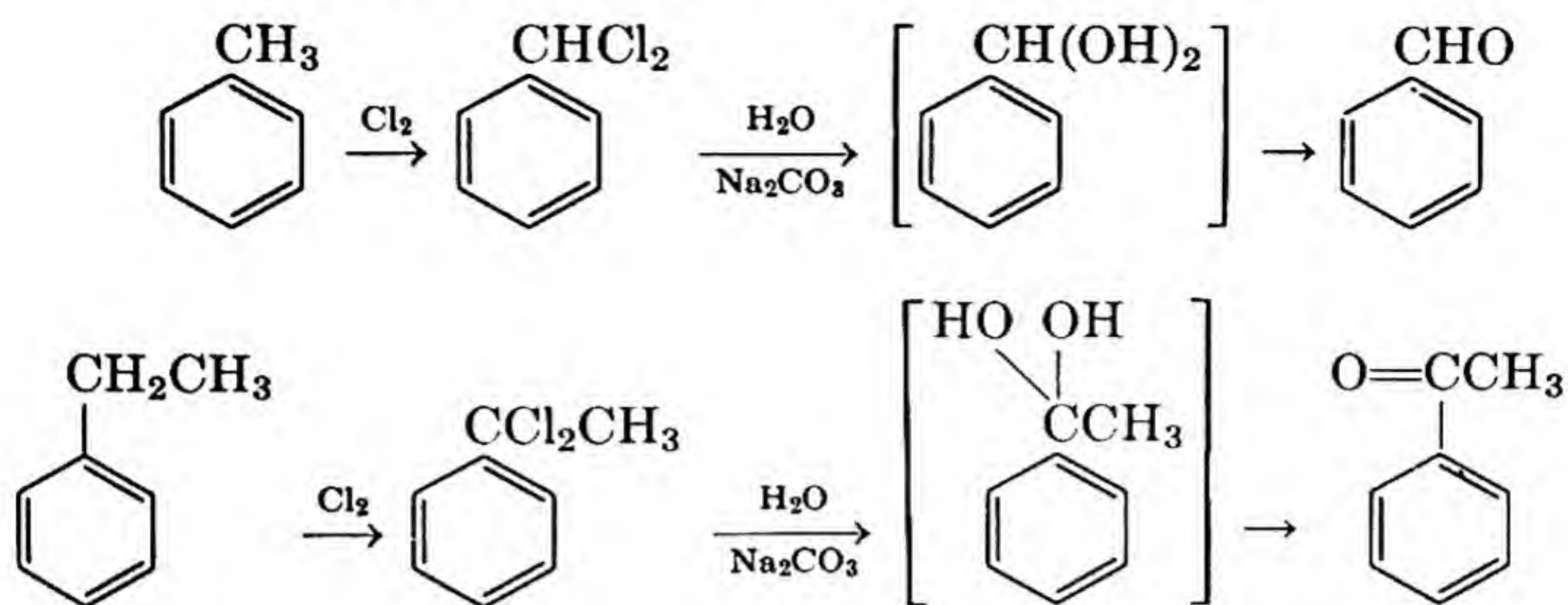
The most frequently used synthetic method for aliphatic aldehydes and ketones consists in the dehydrogenation of primary and secondary alcohols, respectively.



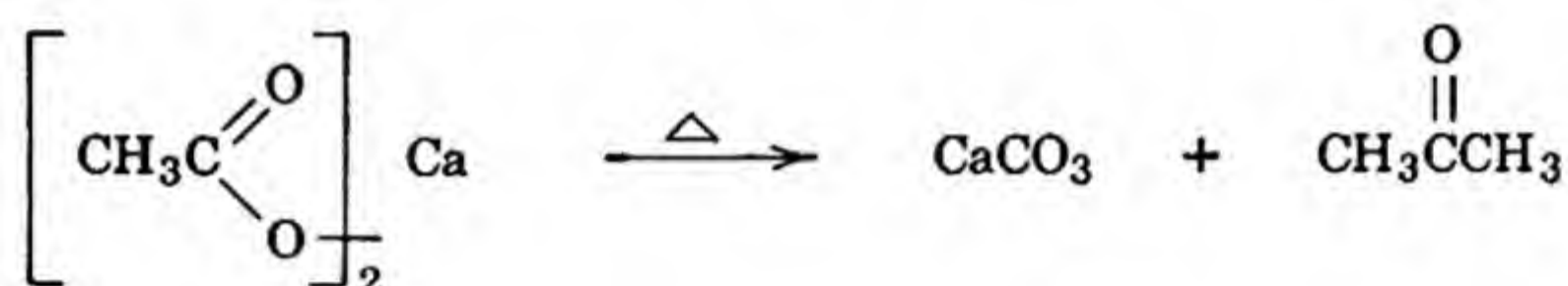
When an oxidizing agent is used in the synthesis of aldehydes it must be recognized that aldehydes readily undergo further oxidation to acids, with the result that the desired aldehyde may be destroyed in the reaction mixture. This can be avoided either by distilling the aldehyde as it is formed or by adding a reagent to the reaction mixture which will react with the aldehyde to give a substance resistant to oxidation. Formaldehyde, acetaldehyde, and acetone are made commercially by catalytic dehydrogenation.



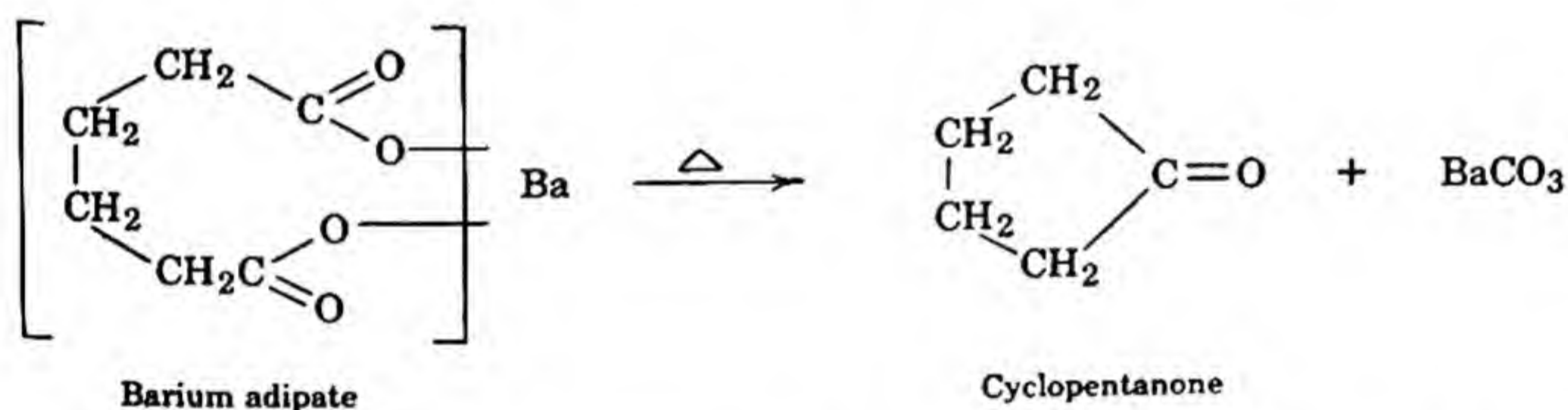
The hydrolysis of dichloro compounds provides a preparative method suitable for certain aromatic aldehydes and ketones. Benzaldehyde and acetophenone can be obtained in this way. This synthesis is not suitable for aliphatic carbonyl compounds because the requisite dichloro compounds are not readily obtained except from aldehydes and ketones.



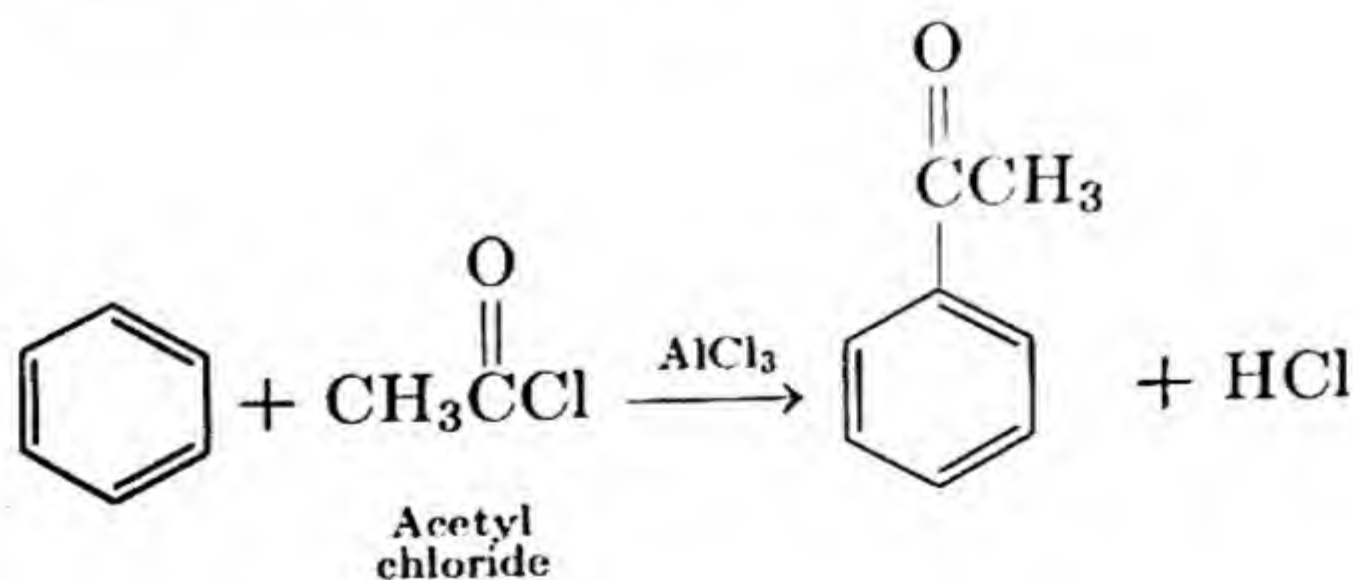
Some ketones are made by heating the salts of acids. For this purpose calcium and barium salts are superior. Acetone, for example,



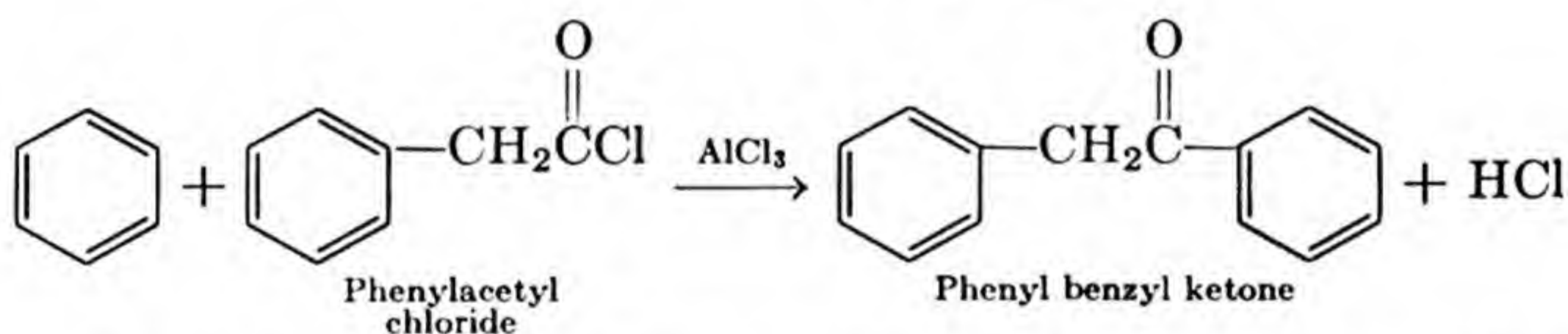
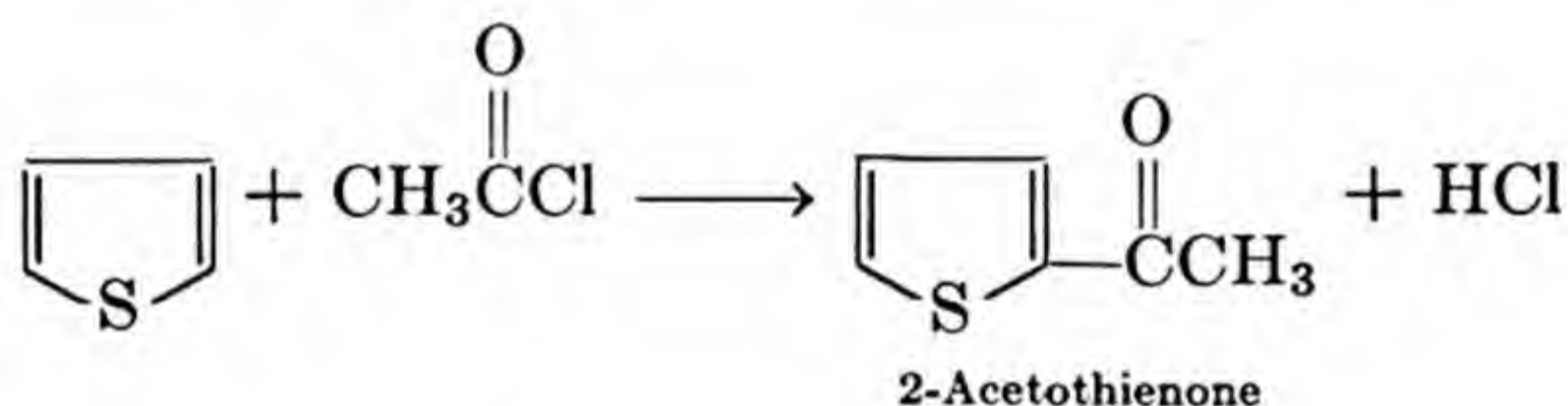
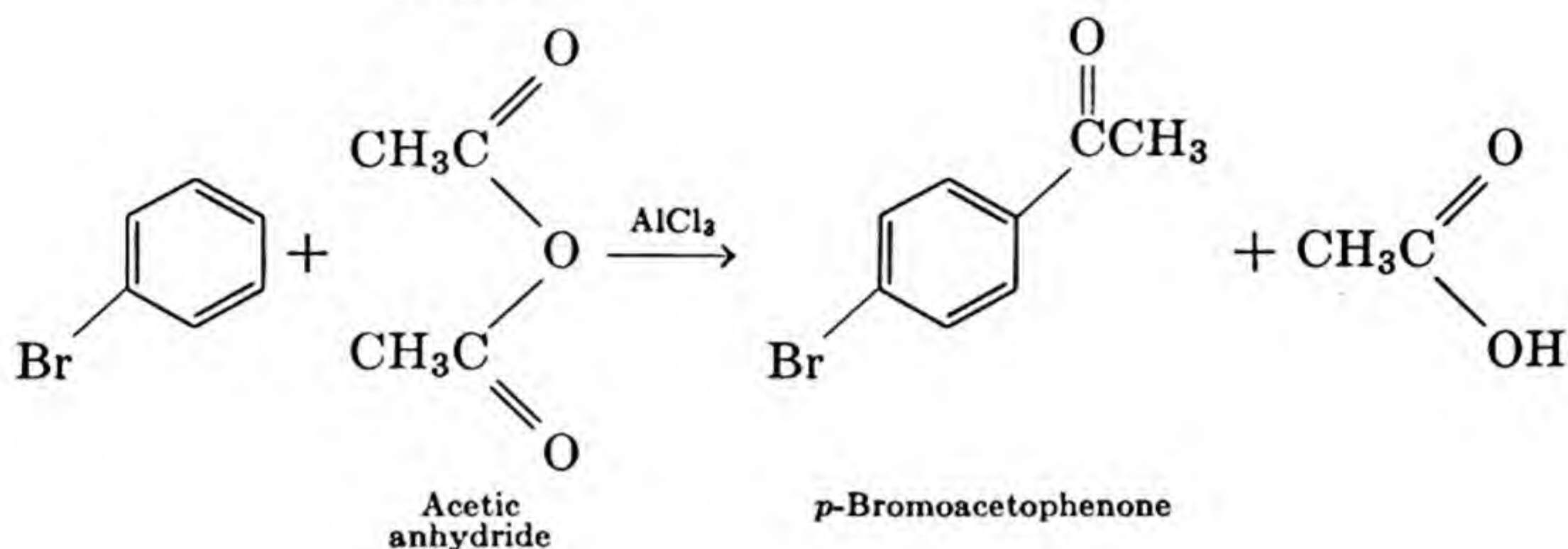
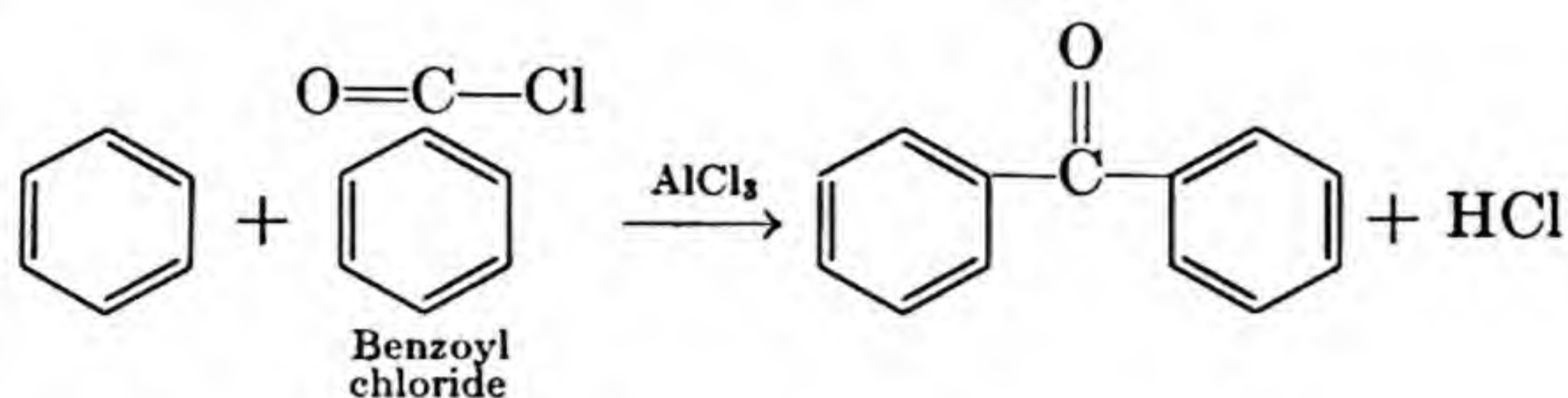
can be prepared by heating calcium acetate. This procedure was formerly an important commercial source of acetone. Another example is provided by the preparation of cyclopentanone.



For the preparation of aromatic ketones the Friedel-Crafts reaction and its modifications are frequently employed. The reactants are an aromatic compound, an acid chloride or anhydride, and a "catalyst," such as anhydrous aluminum chloride. Examples of this reaction are shown in the accompanying equations:

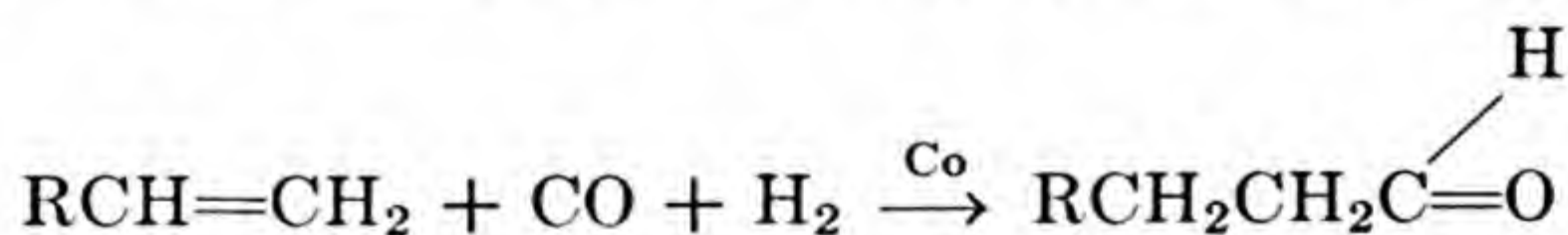






In reality, the aluminum chloride reacts with the ketone to form a stable complex, which must be decomposed with aqueous acid to obtain the ketone. It is not true, therefore, that the aluminum chloride serves as a catalyst only.

In Germany during World War II it was discovered that olefins react with carbon monoxide and hydrogen in the presence of a cobalt catalyst to yield aldehydes. The aldehydes available by this "oxo process" can be converted to alcohols, acids, and their derivatives.



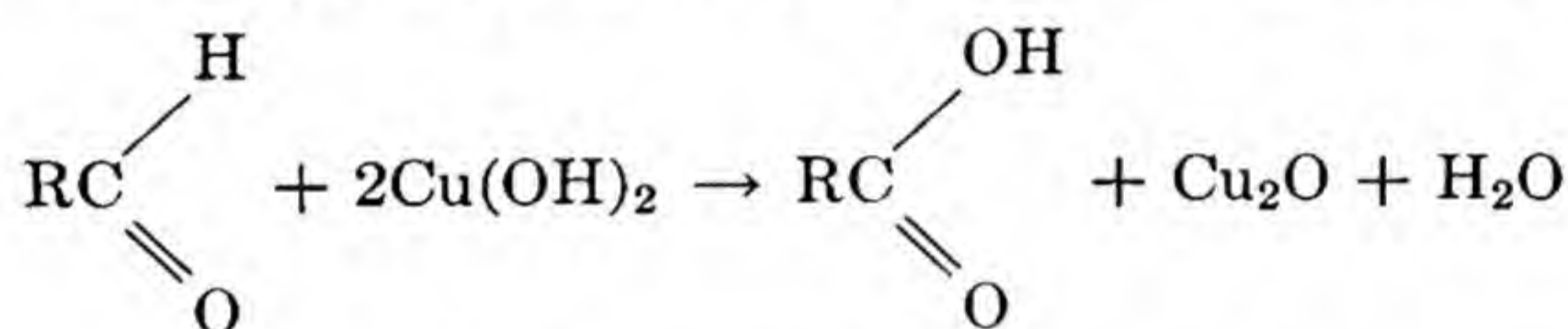
## ► REACTIONS OF CARBONYL COMPOUNDS

The carbonyl group is an extremely reactive one; thus aldehydes and ketones undergo numerous reactions. In general, the reactions

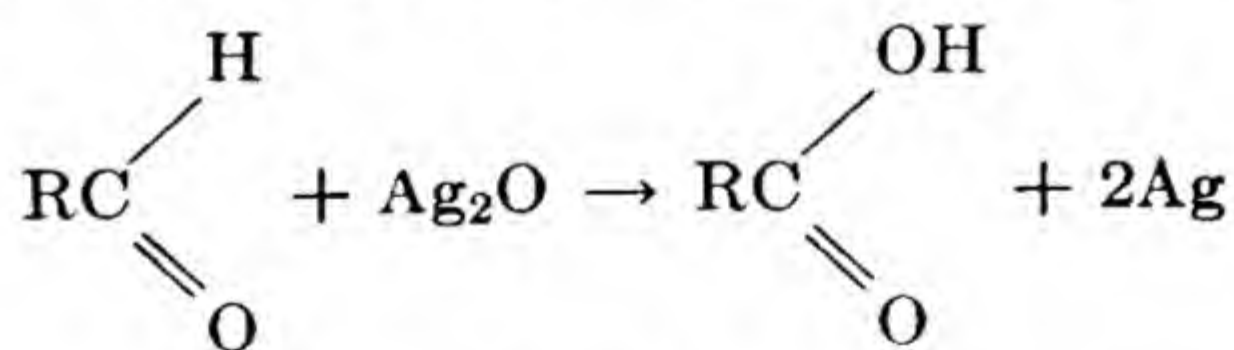


of the two are similar, though the aldehydes are usually more reactive than the ketones. There are a few reactions, however, which only the aldehydes undergo.

**Oxidation of Aldehydes.** It has already been mentioned that aldehydes are readily oxidized, but that the oxidation of ketones requires vigorous conditions, with consequent rupture of the carbon chain. This difference is used as a method for distinguishing aldehydes from ketones in the laboratory. Several different tests apply this principle. Benedict's and Fehling's solutions contain copper sulfate and sodium hydroxide. The cupric ion is a mild oxidizing agent in alkaline solution, but to maintain solubility under these conditions, it is necessary to add a complexing agent, a tartrate in Fehling's solution and a citrate in Benedict's. For simplicity, the reagent in both cases is here represented as cupric hydroxide,  $\text{Cu}(\text{OH})_2$ . A positive test for an aldehyde is indicated by the precipitation of cuprous oxide which is typically reddish brown but occasionally yellow.



Metallic copper may also be produced. In Tollens' test the reagent is prepared from silver nitrate and aqueous ammonia. Though the silver is present in the form of a complex ion, it is customary to write the reagent as silver oxide,  $\text{Ag}_2\text{O}$ . A positive test is indicated by the production of a silver mirror on the walls of the test tube. If the test tube is not sufficiently clean, the silver may separate as a brownish precipitate rather than form a mirror. The Tollens reaction is the basis of the process used in silvering mirrors.



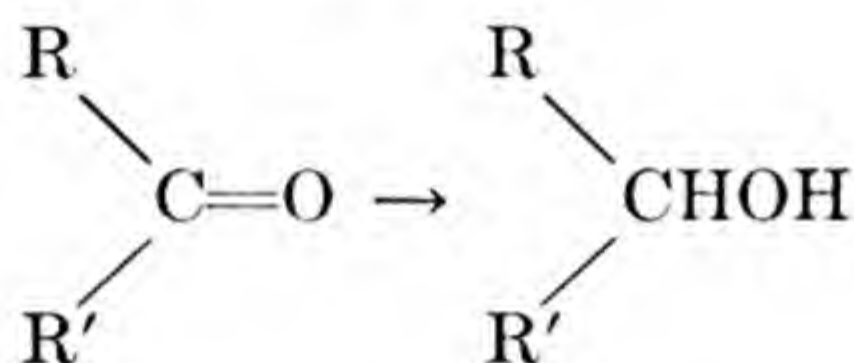
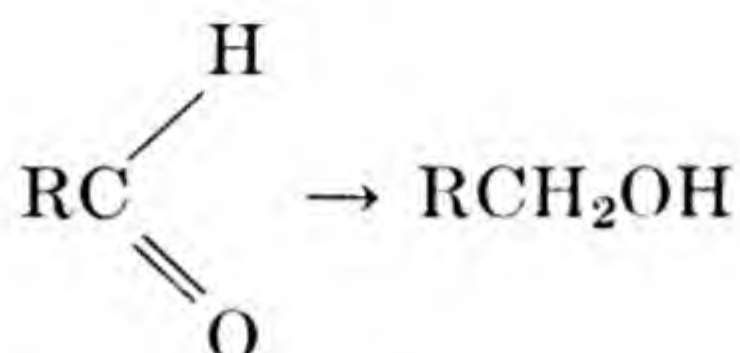
Aldehydes are so readily oxidized that the oxygen of the atmosphere attacks them, though slowly. This process, which occurs with other classes of compounds as well, is called autoxidation.

**Additions to the Carbonyl Group.** A comparison of the carbonyl group,  $\begin{array}{c} \diagdown \\ \text{C}=\text{O} \\ \diagup \end{array}$ , with the double bond,  $\begin{array}{c} \diagdown \\ \text{C}=\text{C} \\ \diagup \end{array}$ , leads us to



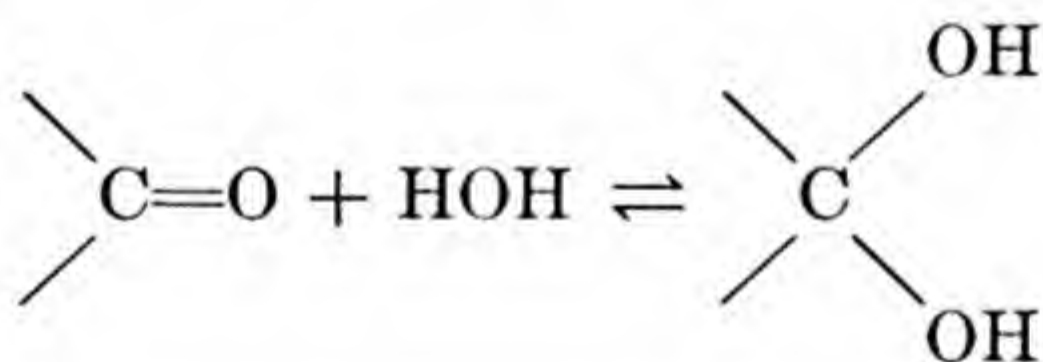
suspect that it would undergo addition reactions. It does so, but the reagents are in general different from those which add to the carbon-carbon double bond. Most are hydrogen-containing reagents, and addition occurs so that the hydrogen atom attaches itself to the oxygen atom. The tendency to undergo a specific addition reaction varies considerably among the carbonyl compounds.

Aldehydes and ketones undergo reduction to yield primary and secondary alcohols, respectively. The reaction can be considered to

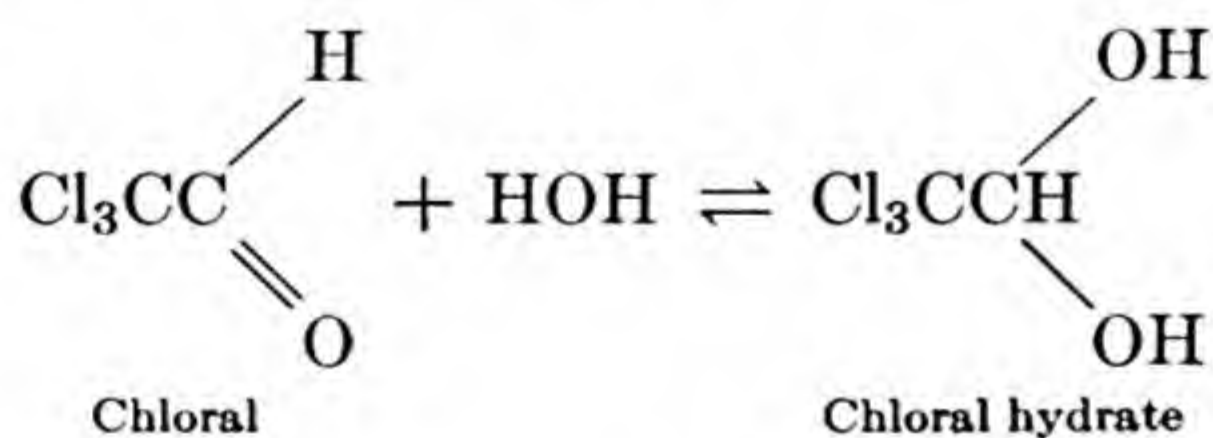


be addition across the  $\begin{array}{c} \diagdown \\ \text{C}=\text{O} \\ \diagup \end{array}$  bond. Reagents which accomplish this transformation are hydrogen with a catalyst such as platinum, sodium and an alcohol, and lithium aluminum hydride ( $\text{LiAlH}_4$ ).

Carbonyl compounds have a tendency to react with water.

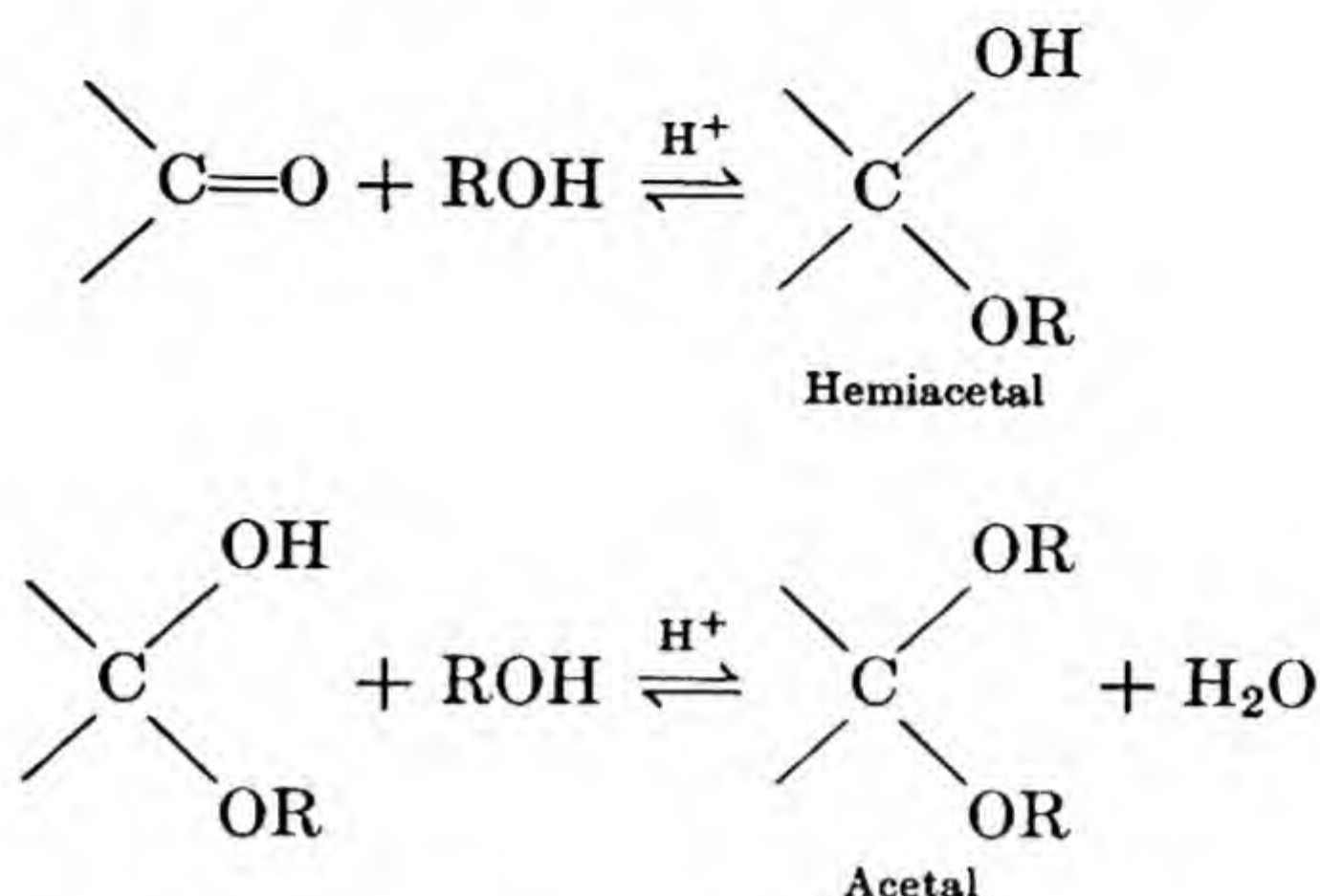


In nearly every case the equilibrium is far to the left. Expressed in another way, compounds having two hydroxyl groups on the same carbon atom are unstable. Chloral hydrate is an exception.



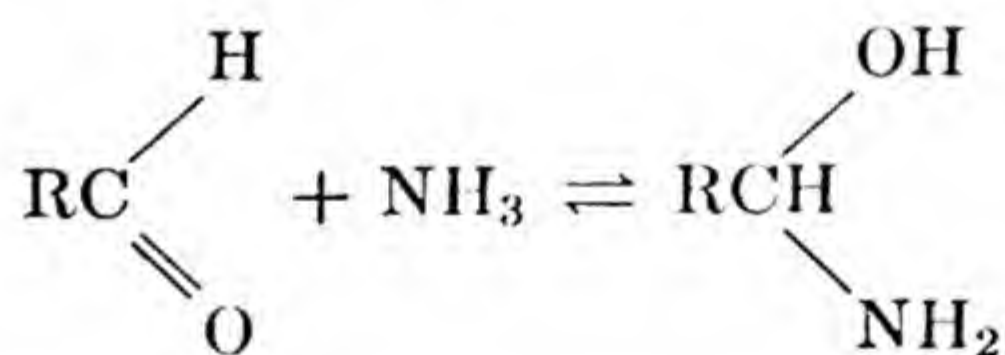
Like water, alcohols combine with the carbonyl compounds to give compounds called hemiacetals. The reaction is catalyzed by strong

acids, but such catalysts bring about further reaction of the hemiacetal with another molecule of alcohol, and an acetal is produced.

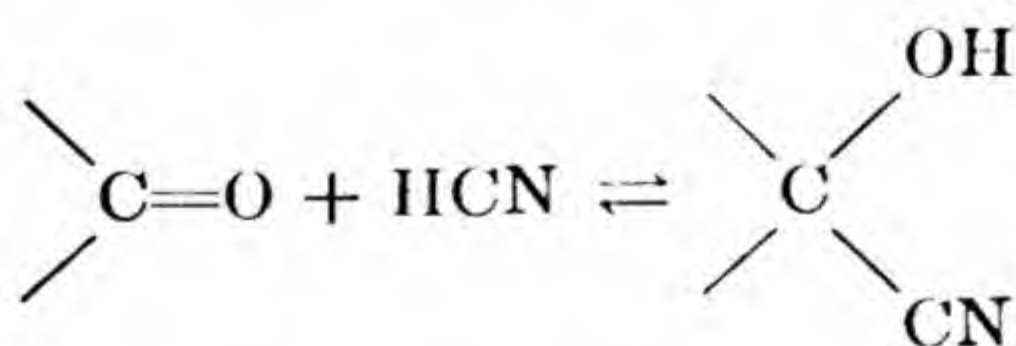


Hemiacetals revert readily to the carbonyl compound and alcohol, and, in fact, few have been isolated. Acetals, on the other hand, are stable in neutral and alkaline solution, though readily hydrolyzed by aqueous acids. This difference in stability is important in understanding the behavior of the carbohydrates (Chapter 13). In general, aldehydes form stable acetals, but with most ketones the equilibrium is so far to the left that direct conversion to the acetals is impossible.

Aldehydes, with the exception of formaldehyde, undergo reaction with ammonia to give aldehyde-ammonias, which are useful in synthesis.

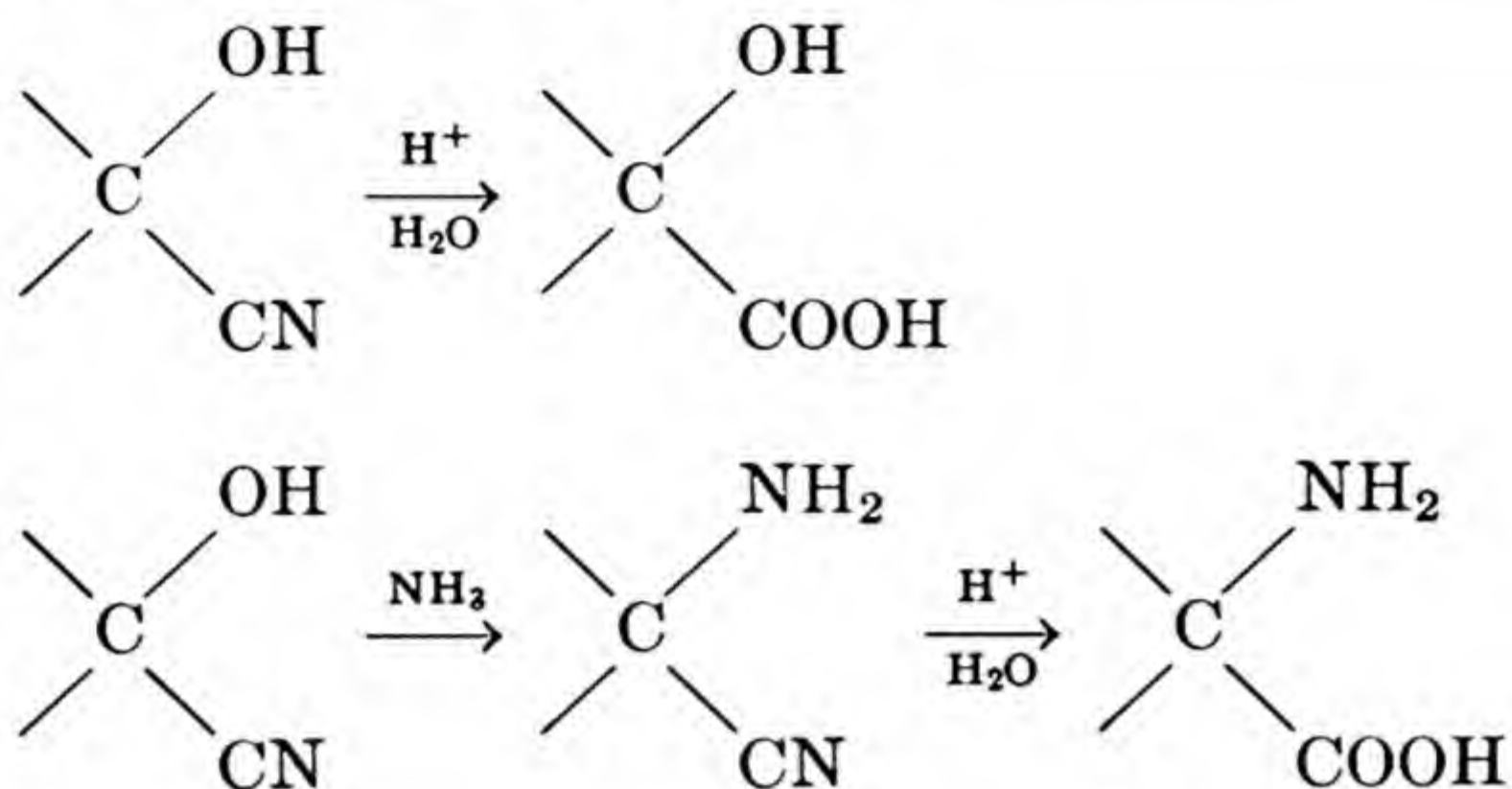


Hydrogen cyanide adds to aldehydes and some of the lower ketones to give cyanohydrins. These products, too, are useful in organic

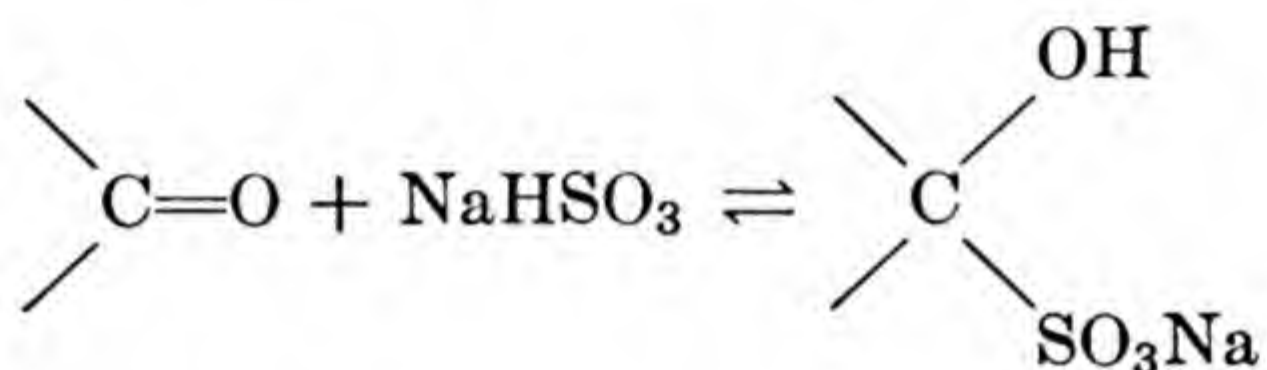


synthesis. For example, they can be hydrolyzed to give hydroxy acids. Treatment of the cyanohydrins with ammonia produces aminonitriles, which can be hydrolyzed to amino acids (Chapter 15).

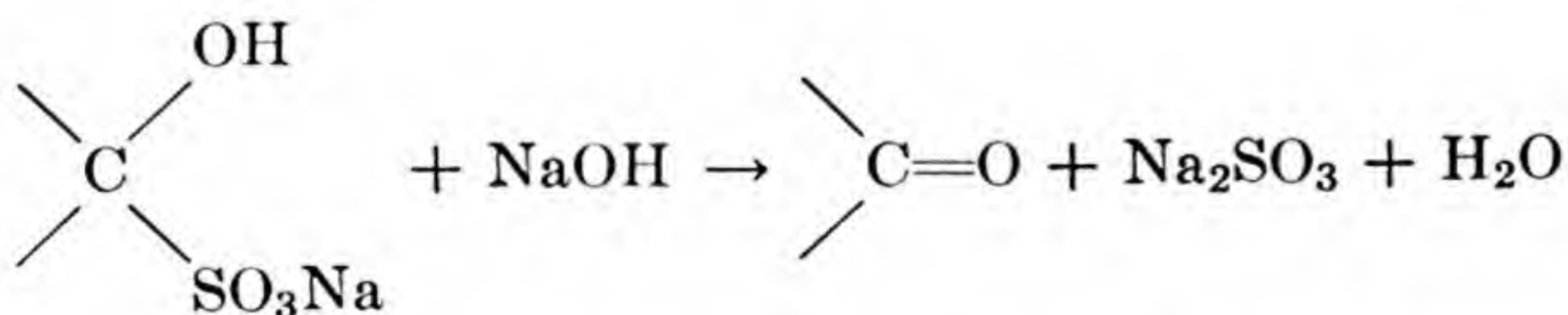
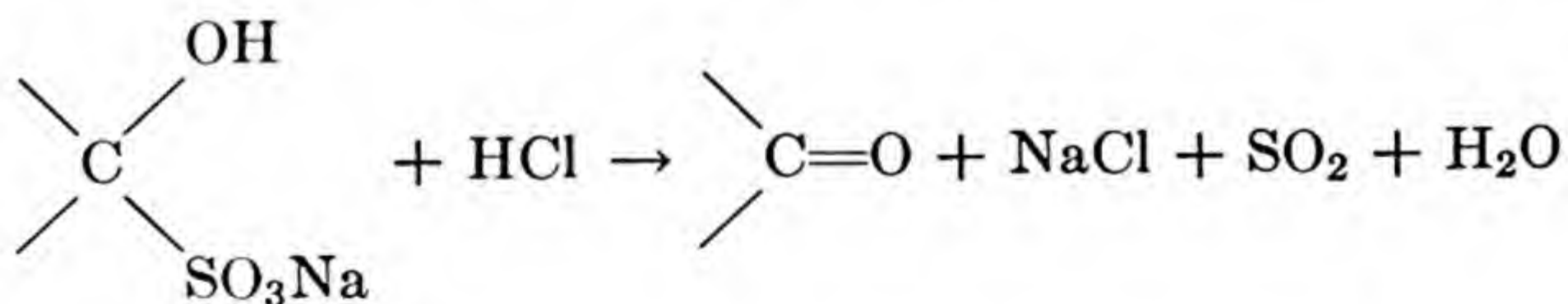




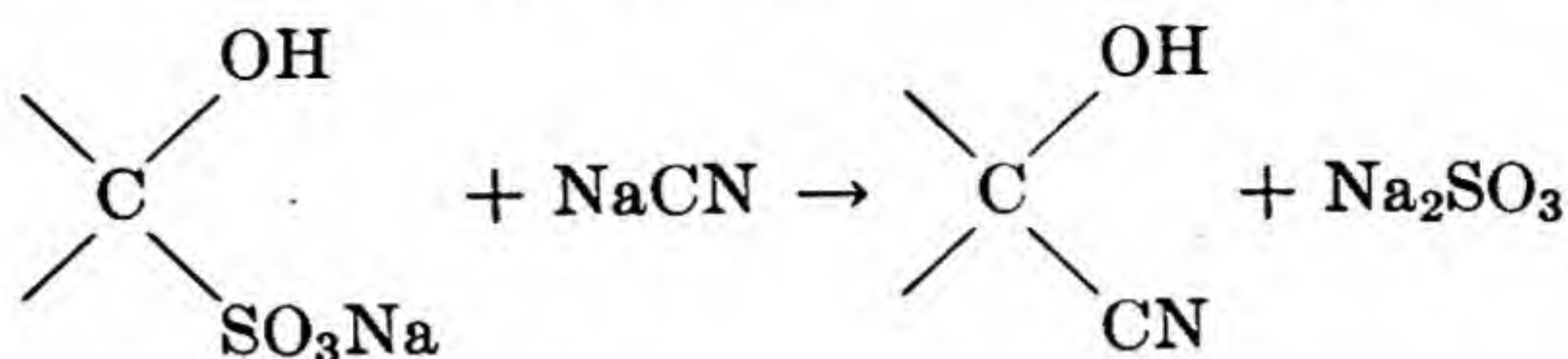
Aldehydes, certain methyl ketones, and a few cyclic ketones (in which the carbonyl group is part of a ring) react with sodium bisulfite to give the so-called bisulfite addition products.



Usually, the reaction is brought about by shaking the carbonyl compound with a saturated aqueous sodium bisulfite solution. The product is salted out as a white solid by the excess sodium bisulfite present. The formation of these substances is useful in the identification of organic compounds and in the isolation of carbonyl compounds from mixtures. When such a mixture is shaken with the bisulfite, a reactive carbonyl compound forms the bisulfite addition product which can be separated easily. The product can then be treated with acid (preferably) or alkali, which regenerates the carbonyl compound.

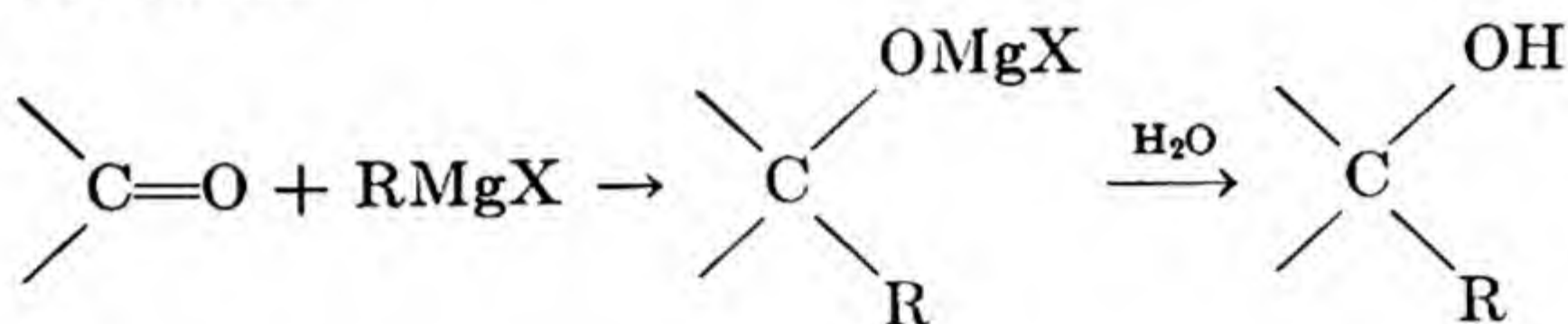


The bisulfide addition products react with sodium cyanide to give cyanohydrins.

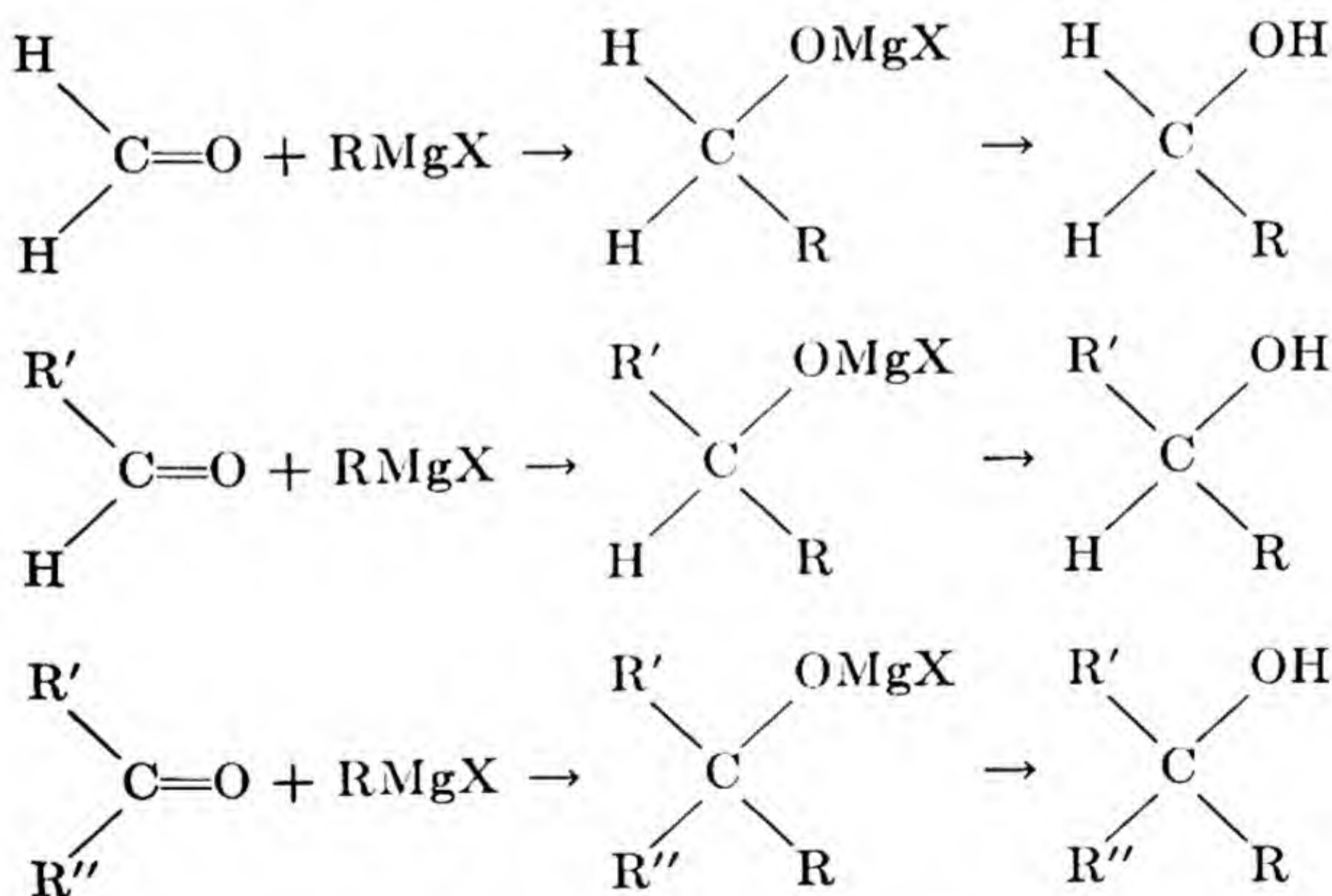


This method is often employed to prepare cyanohydrins because it avoids the use of hydrogen cyanide, a very poisonous gas.

A reaction widely employed in the organic laboratory for the synthesis of alcohols is the addition of Grignard reagents to carbonyl compounds. The adducts are actually halomagnesium salts, but treatment with water yields the alcohols. The reaction can be generalized as follows.

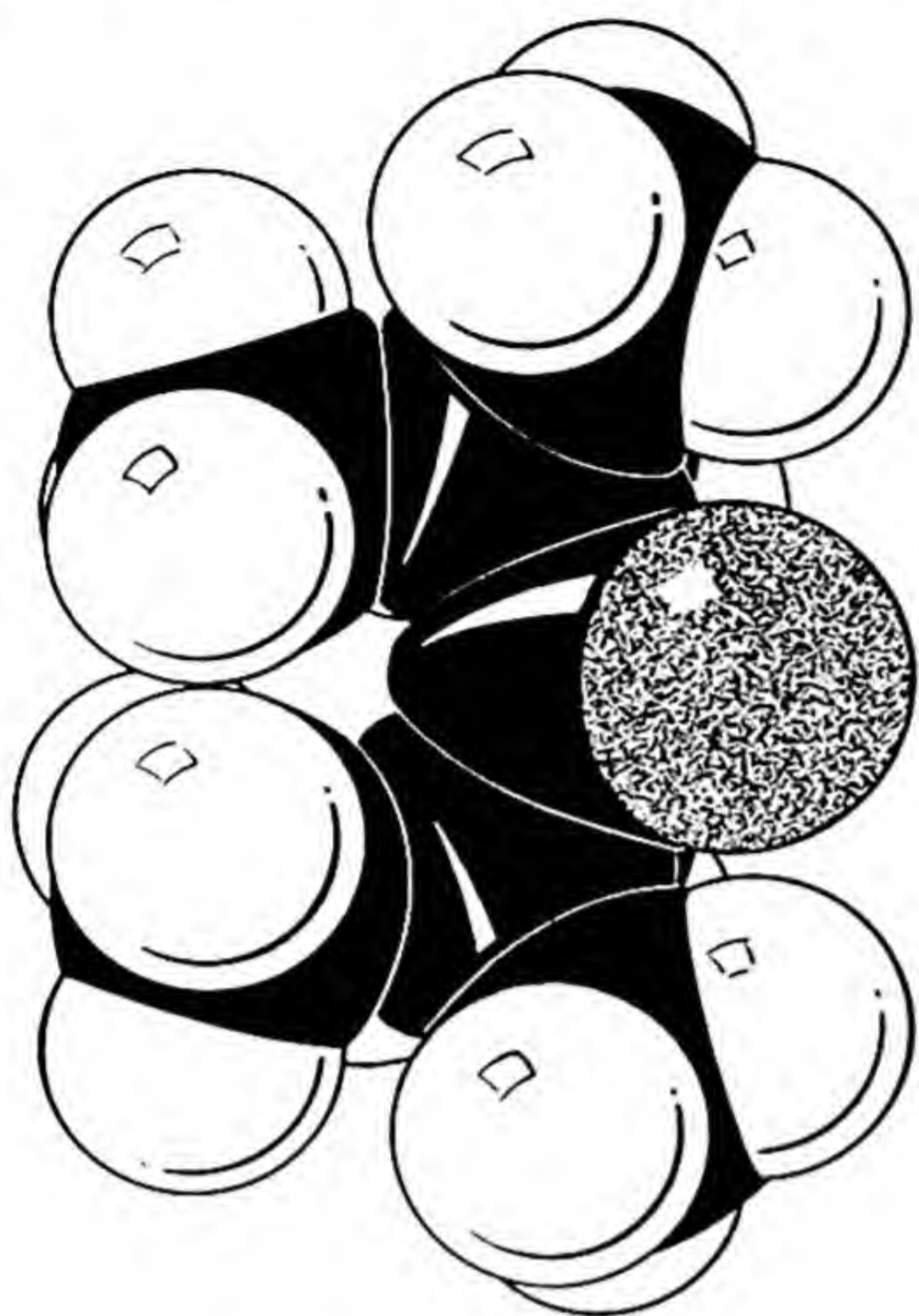


The type of alcohol obtained depends upon the carbonyl compound chosen. Formaldehyde yields primary alcohols, other aldehydes give secondary alcohols, and ketones furnish tertiary alcohols.



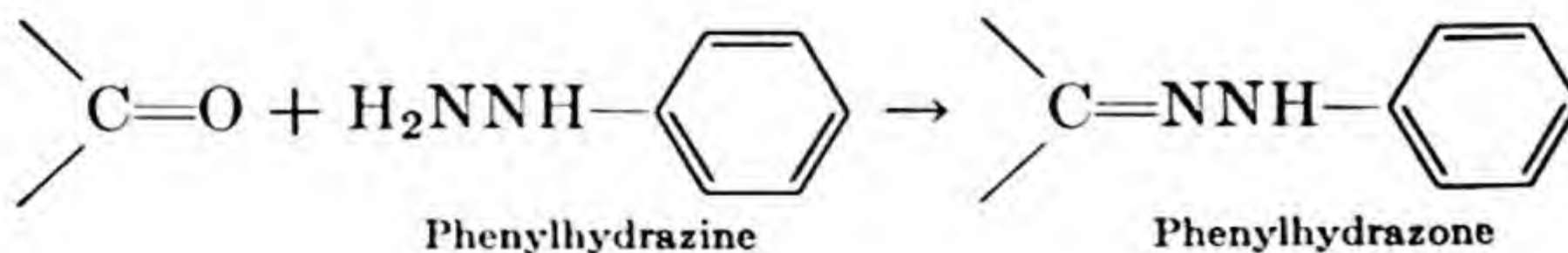
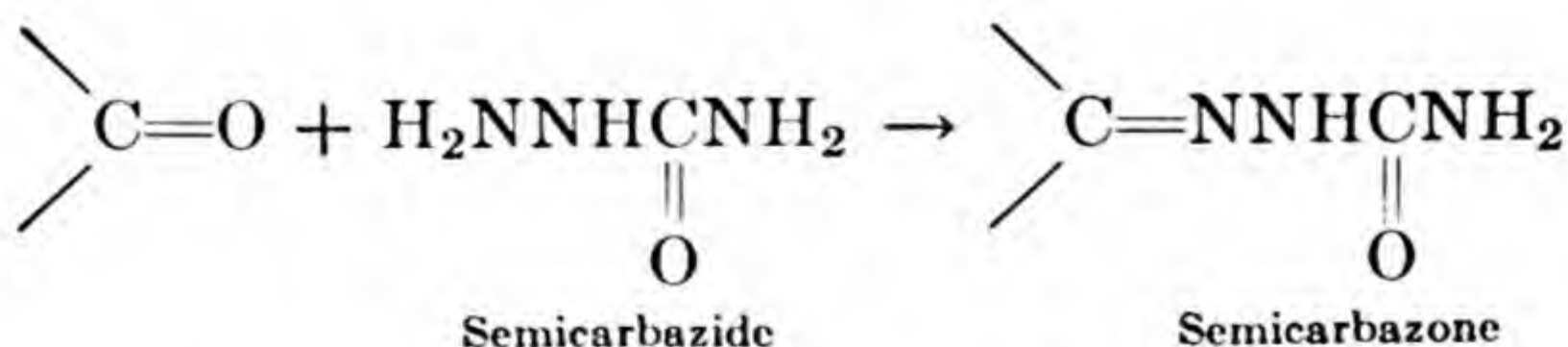
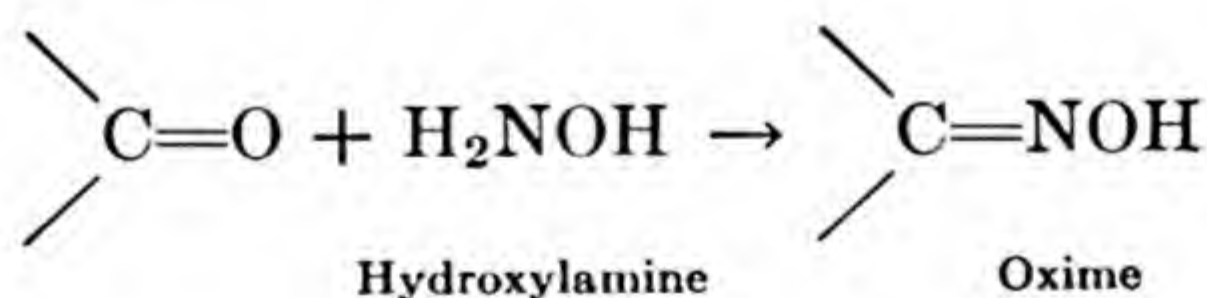
The preparation of a tertiary alcohol by this method can usually be accomplished in alternative ways. For example, 2-phenyl-2-butanol could be prepared from methyl ethyl ketone and phenylmagnesium bromide, acetophenone and ethylmagnesium bromide, or propiophenone and methylmagnesium iodide.

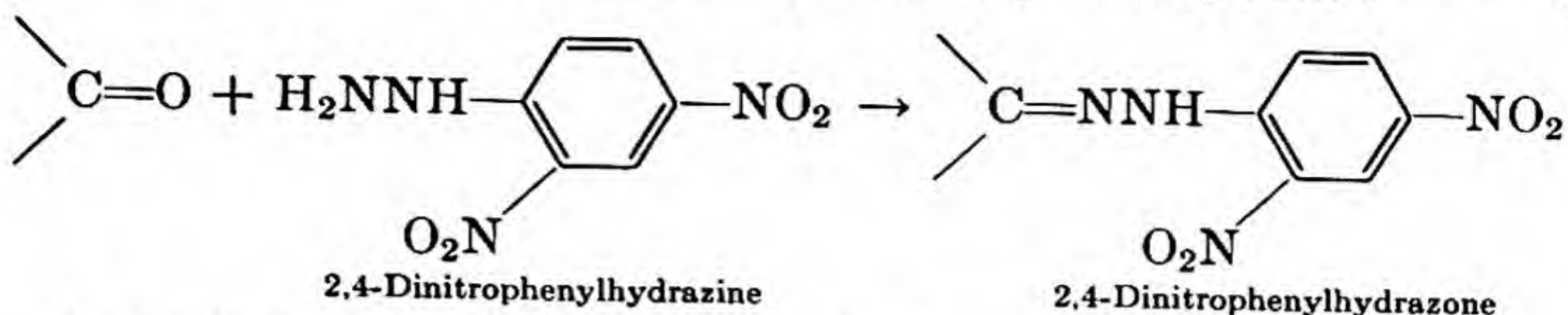


*Di-*t*-butyl ketone*

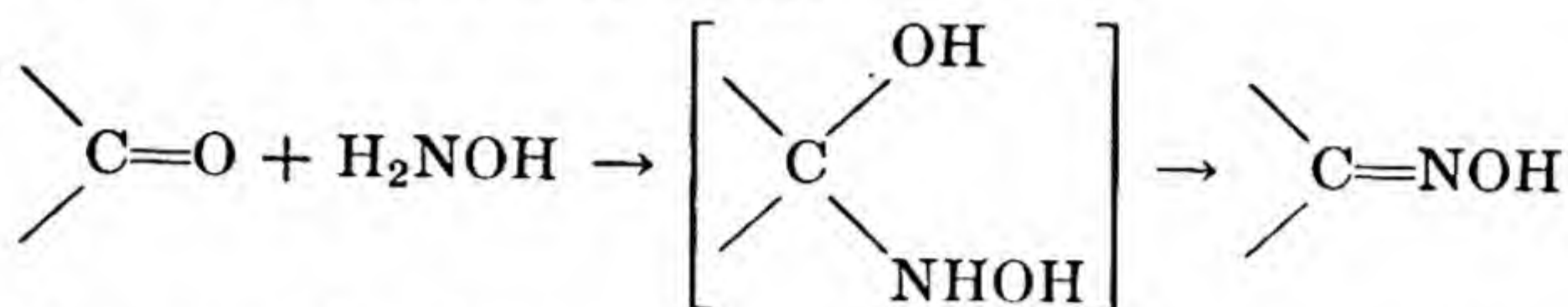
A ketone such as di-*t*-butyl ketone does not react with the ordinary carbonyl reagents because the carbonyl group is screened by the bulky *t*-butyl groups, rendering the entrance of the reagent difficult.

**Condensation Reactions of Aldehydes and Ketones.** Though the meaning of the term “condensation reaction” has been broadened considerably, it is usually taken to mean a reaction in which a new carbon-carbon or carbon-nitrogen bond is formed and in which some small molecule is eliminated. Aldehydes and ketones generally undergo condensation with certain nitrogen-containing bases to form solid compounds which are useful in identification. The formation of a number of the products more commonly employed for this purpose is shown here.

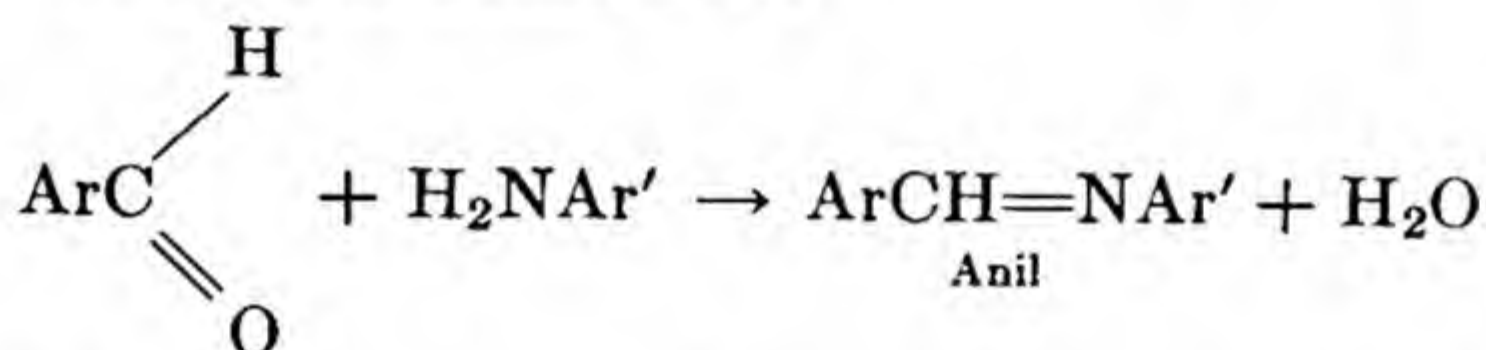




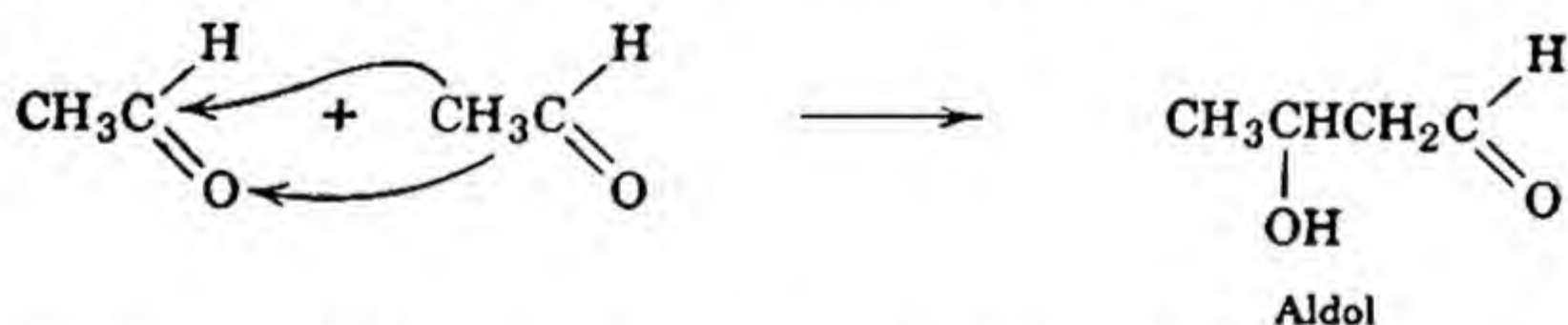
It is likely that the reaction in all these examples occurs first by addition, followed by loss of water.



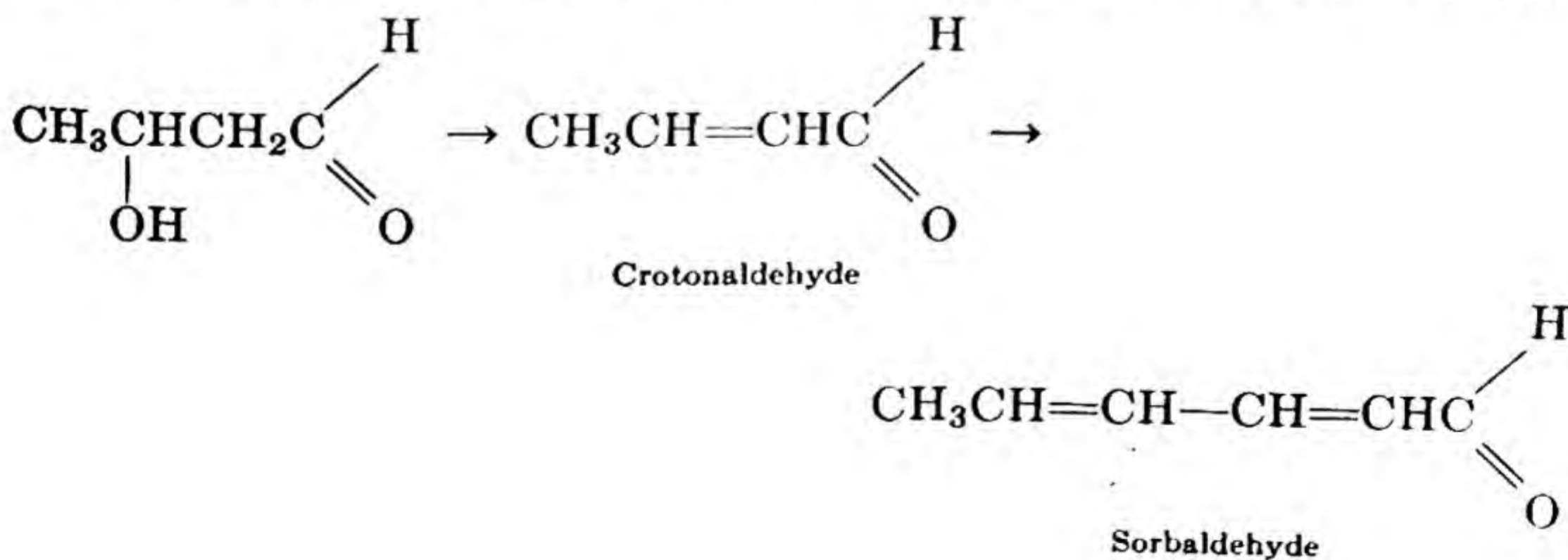
Another example of a condensation reaction is that between an aromatic aldehyde and an aromatic primary amine (Chapter 14), which yields an anil, or Schiff base.



**The Aldol Condensation and Cannizzaro Reaction.** One of the most noteworthy of aldehyde reactions is the aldol condensation. An example is the reaction of acetaldehyde with a base. Two molecules take part to give the hydroxyaldehyde aldol. Inspection reveals that this reaction involves an addition of one molecule of the alde-

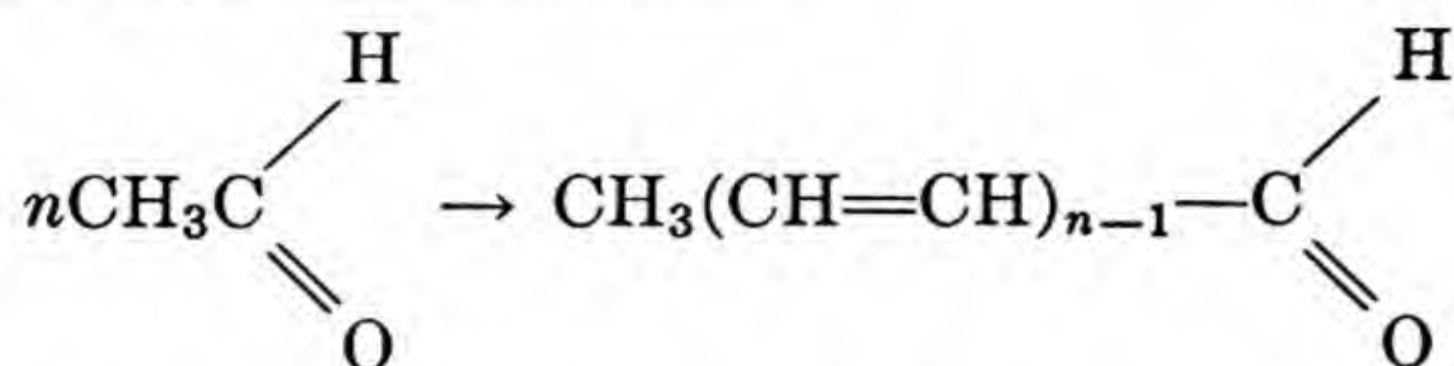


hyde to another. Aldol can lose a molecule of water under the conditions of the reaction to form crotonaldehyde, which can condense with an additional molecule of acetaldehyde. The process can con-

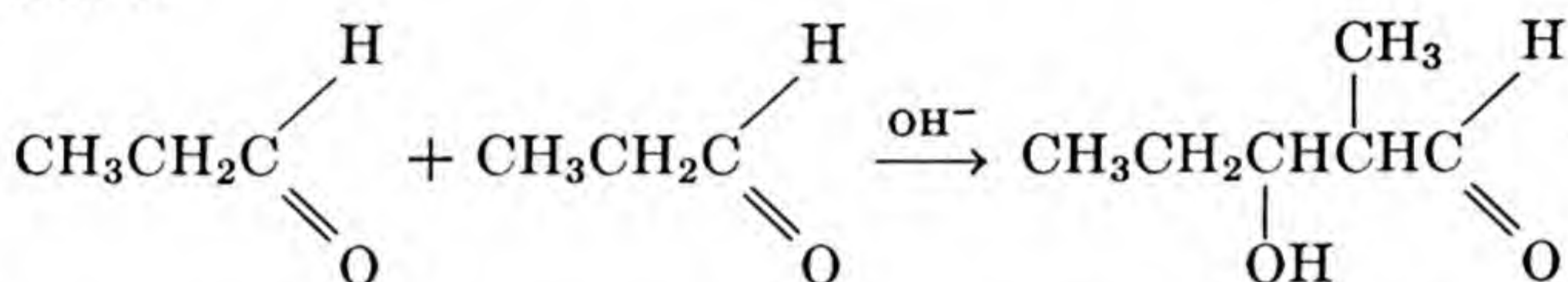




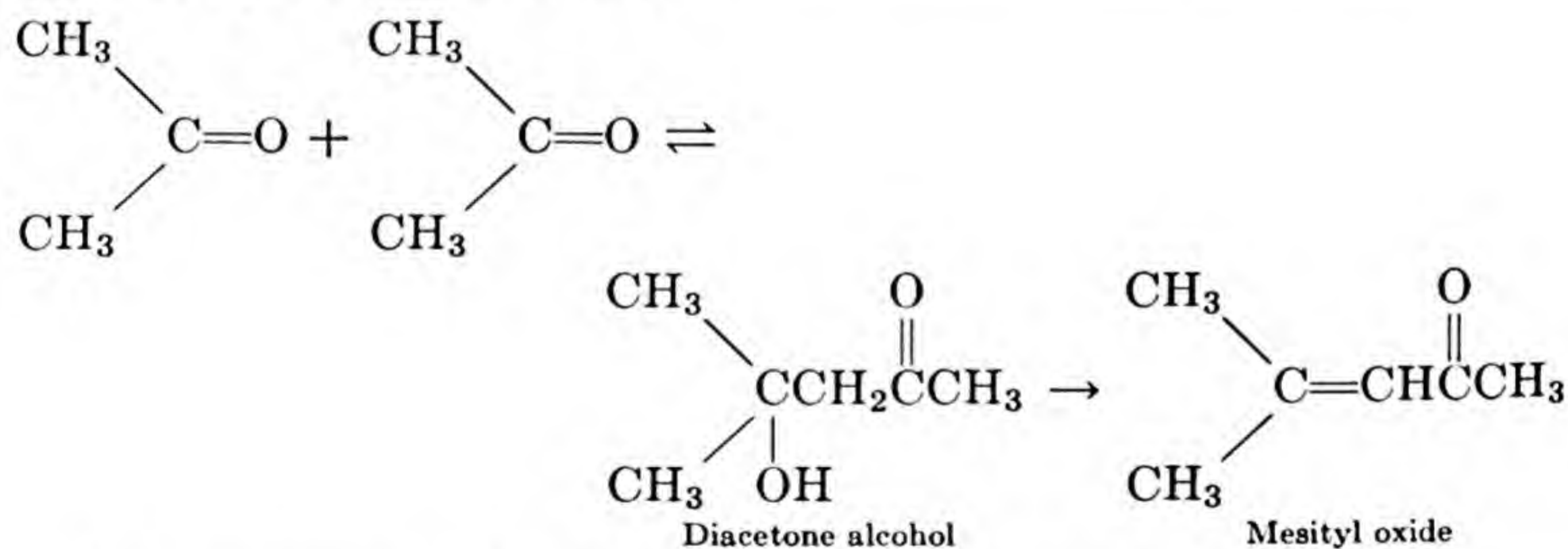
tinue if the reaction mixture is warm, and the final product is polymeric, the so-called aldehyde resin.



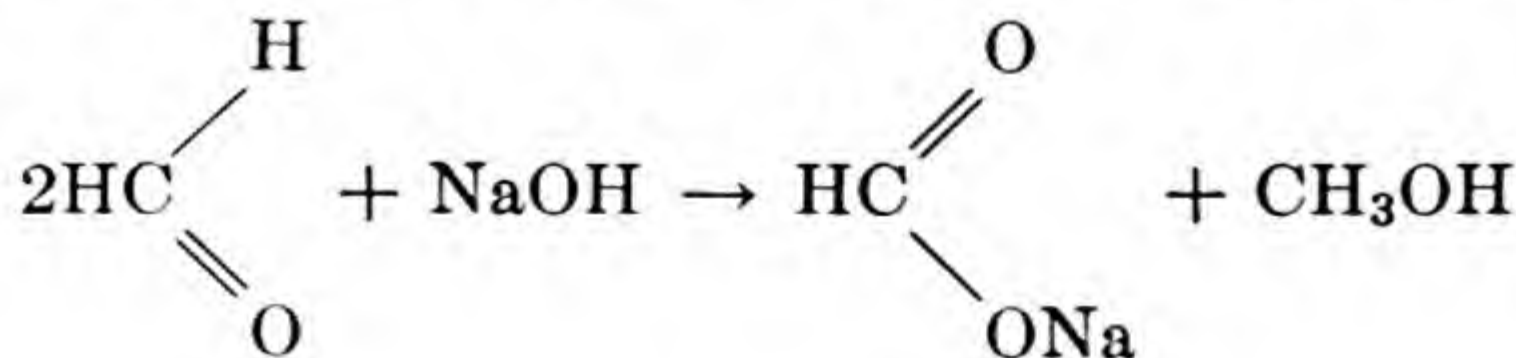
Propionaldehyde can also undergo the aldol condensation, as does any aldehyde having *hydrogen attached to the carbon atom holding the aldehyde group*. In general, the carbon atom holding a functional group is said to be the alpha ( $\alpha$ ) carbon atom, and hydrogen attached thereto is said to be  $\alpha$ -hydrogen. Only an  $\alpha$ -hydrogen atom can be involved in the aldol condensation. Thus, with propionaldehyde, the reaction is

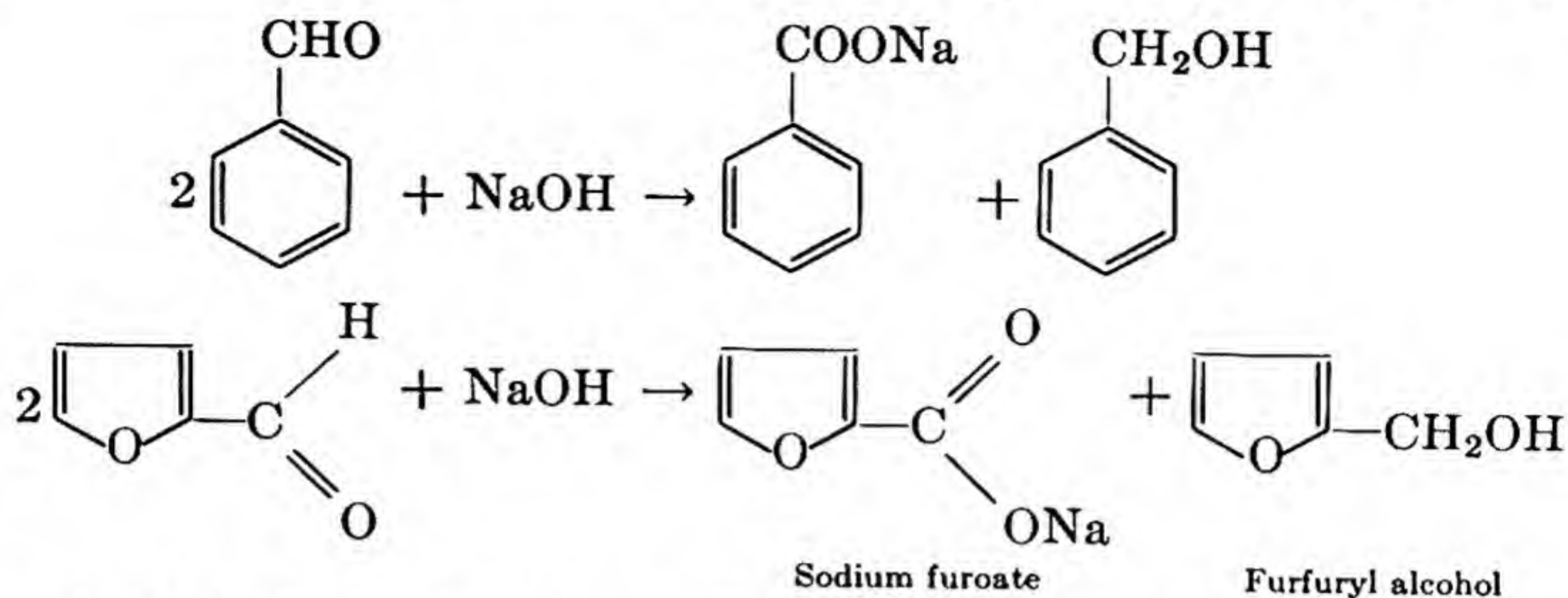


Ketones undergo the reaction, but less readily. The addition step of the process is an equilibrium, and with ketones the equilibrium point is more toward the unchanged ketone. Under special conditions, however, the reaction can be useful. With acetone, for example, it proceeds as follows:



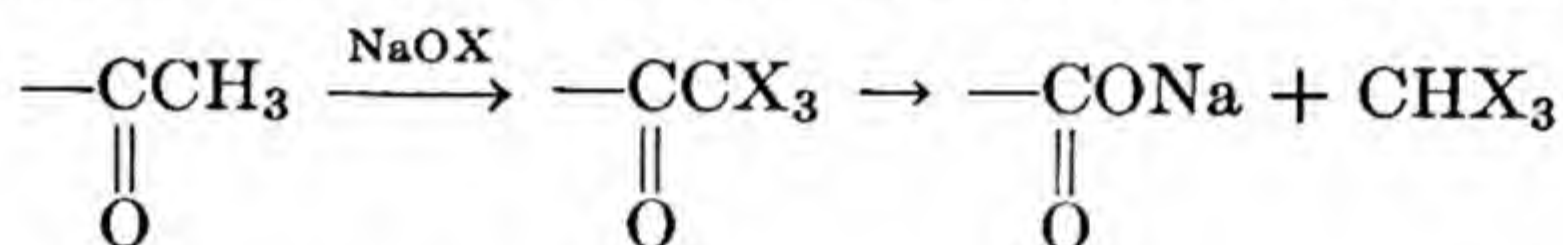
In the presence of bases aldehydes not having  $\alpha$ -hydrogen atoms undergo a peculiar transformation known as the Cannizzaro reaction. Two molecules of aldehyde react; one is oxidized and one is reduced, so that an acid (actually the salt) and an alcohol are formed.



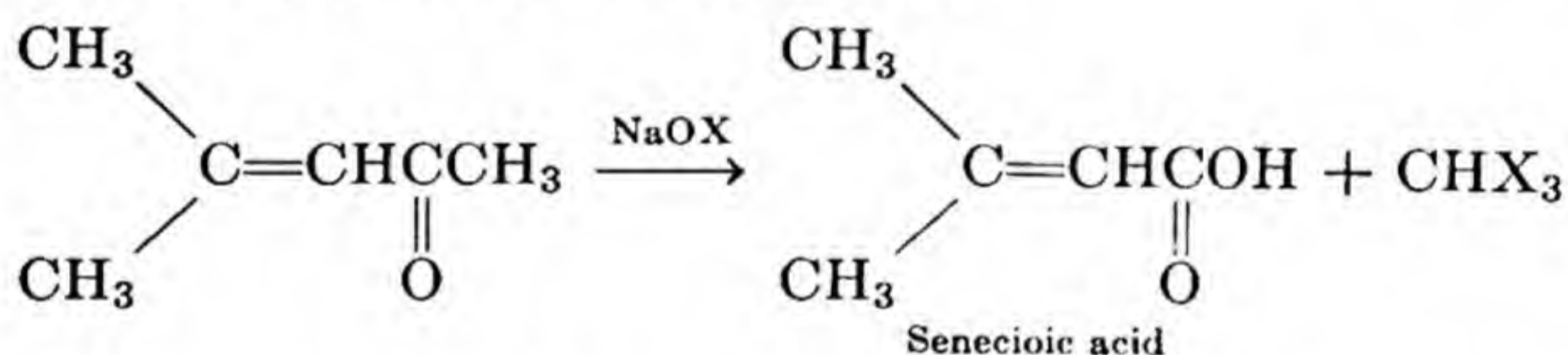


**The Haloform Reaction.** Compounds having the group  $\text{—CCH}_3$   
 $\parallel$   
 $\text{O}$

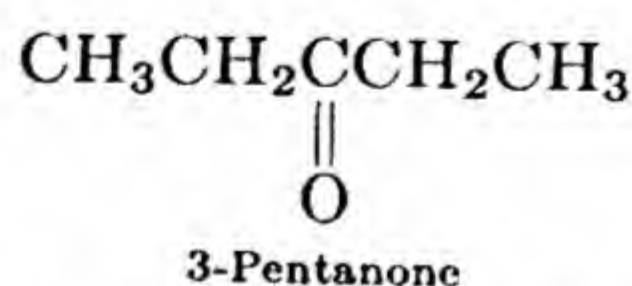
attached to hydrogen or carbon undergo a reaction with sodium hypohalites known as the haloform reaction, so-called because one of the products is a haloform,  $\text{CHX}_3$ . The other product is the salt of an acid with one less carbon atom than the original substance.



The reaction is useful for the preparation of haloforms and, in some special cases, acids, such as senecioic acid.



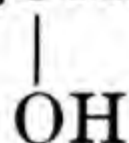
It is also employed in the iodoform test for identification purposes. Sodium hypoiodite is the reagent, and a positive test is indicated by the production of iodoform, a yellow solid with a characteristic odor. The only carbonyl compounds that give positive tests are acetaldehyde and the methyl ketones. Thus, isomers can, in some cases, be distinguished. 2-Pentanone, for example, gives a positive test, whereas with 3-pentanone the test is negative.



Because sodium hypoiodite is a strong oxidizing agent capable of oxidizing primary and secondary alcohols certain of these compounds also give positive tests. They include ethyl alcohol, which is con-



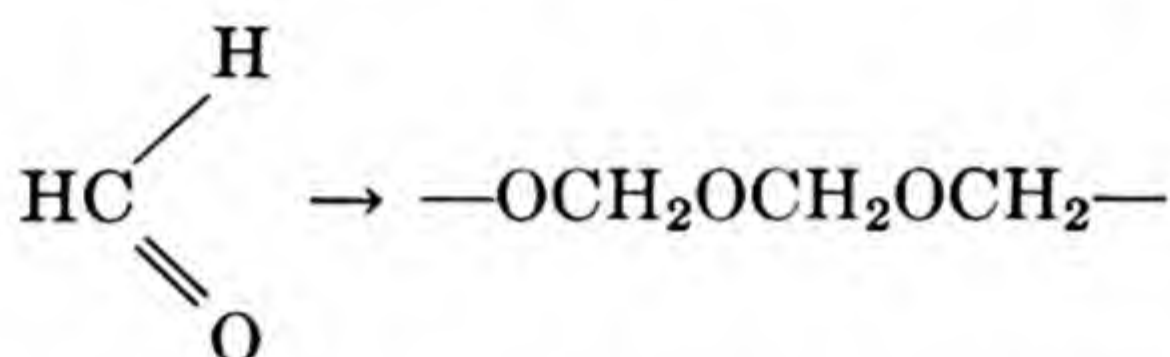
verted to acetaldehyde by the reagent, and alcohols of the type  $\text{CH}_3\text{CHR}$ , which are converted into methyl ketones.



## ► INDIVIDUAL CARBONYL COMPOUNDS

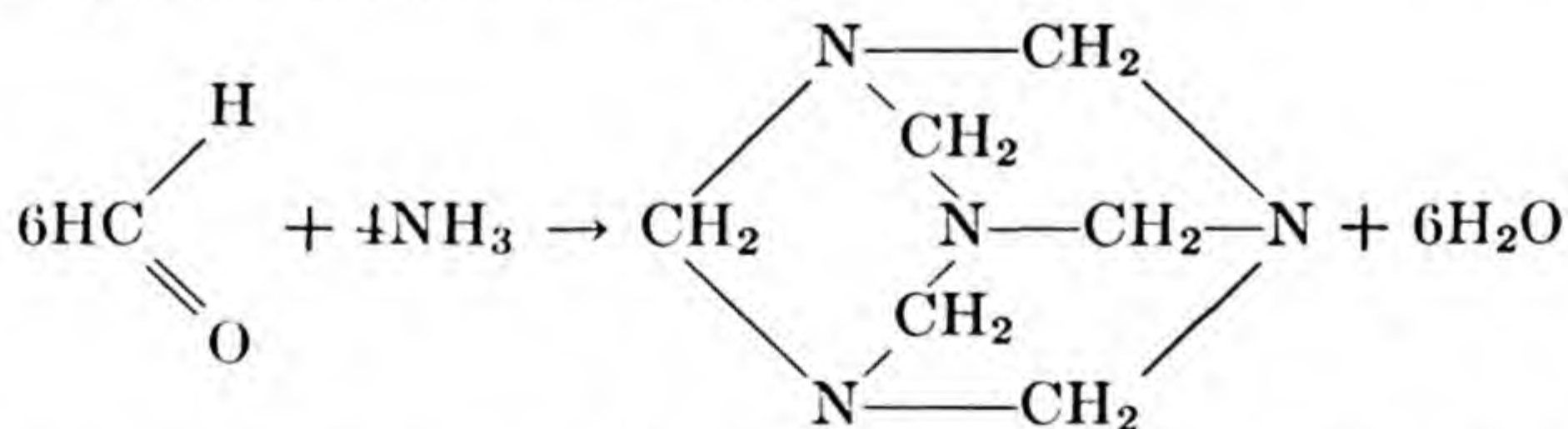
A few aldehydes and ketones are here accorded separate treatment because of their importance as commercial materials or because of some special properties possessed by them.

**Formaldehyde.** Formaldehyde, the simplest aldehyde, is a gas of strong and irritating odor. It is usually sold in a 37–40% water solution called formalin. If formalin is evaporated slowly, paraformaldehyde, a white solid, which is a polymer of formaldehyde, remains.

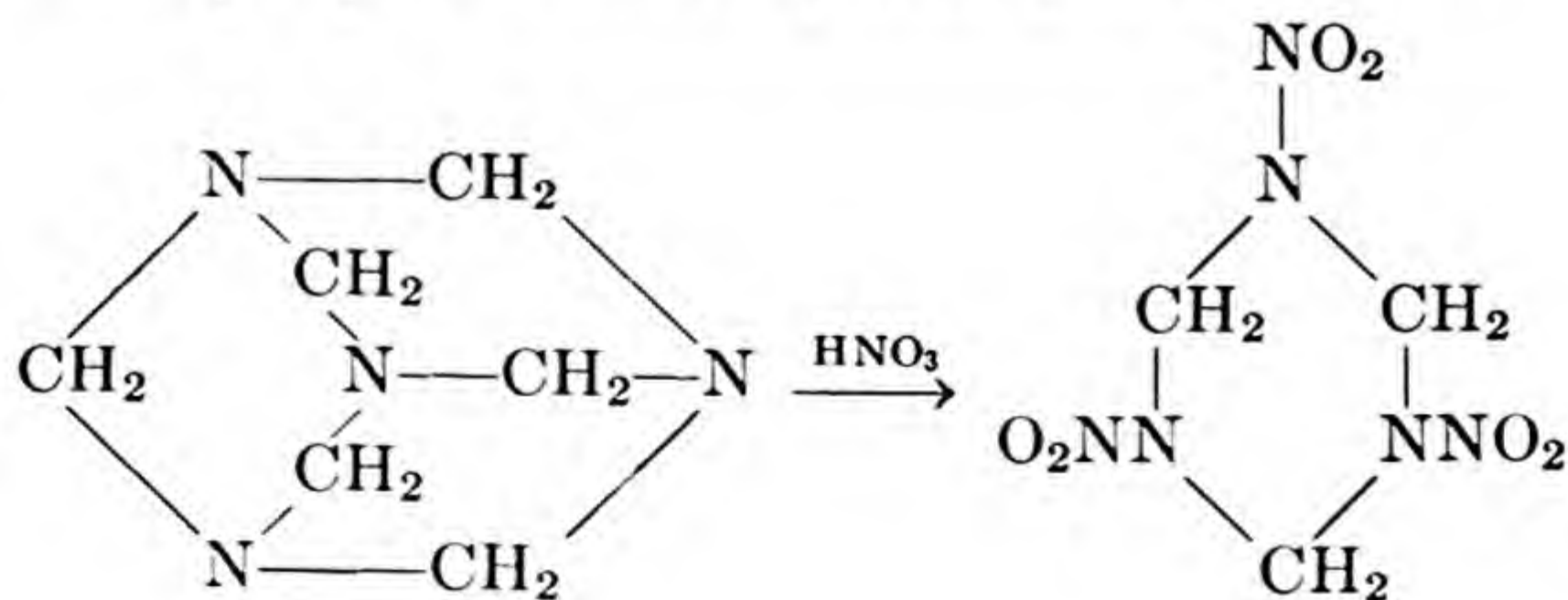


Heating paraformaldehyde causes depolymerization, and since formaldehyde is poisonous to insects it provides a convenient method for the fumigation of rooms.

When formalin is heated with aqueous ammonia a solid known as hexamethylenetetramine is formed.



This compound is used in the manufacture of Bakelite and in the preparation of amines. Nitric acid with hexamethylenetetramine yields a military explosive called cyclonite, or RDX.



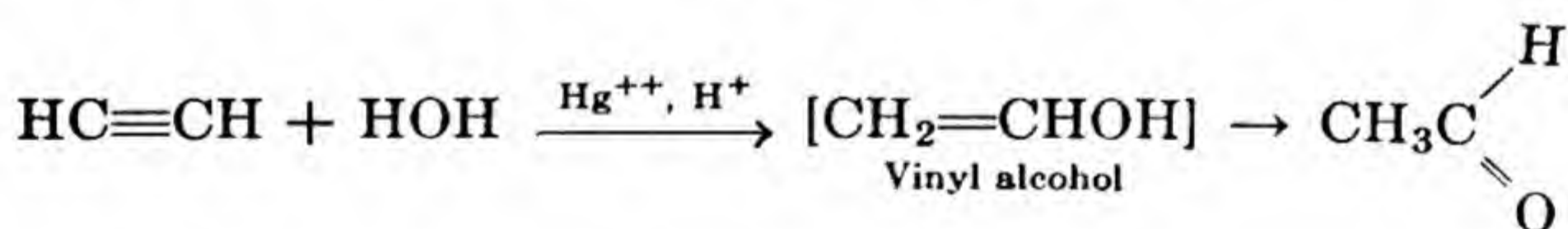


Formaldehyde reacts with proteins to give more rigid materials which are not attacked so readily by insects and microorganisms as the original proteins. For this reason, formalin is employed for zoological preservation and in embalming fluids. It has also been used for preserving milk, but because it is toxic to man this application is generally condemned.

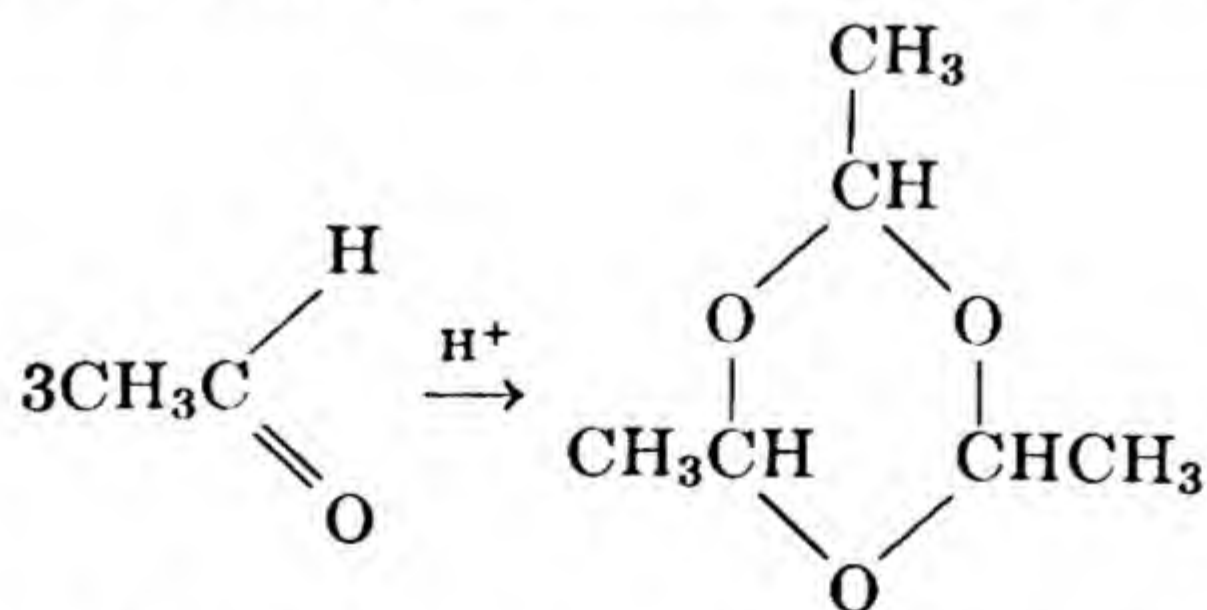
If an acid solution of ferric chloride is warmed with milk containing formaldehyde, a violet color appears. This test is specific for formaldehyde and is very sensitive; 1 part of formaldehyde in 200,000 can be detected in this way. Another method for the detection of formaldehyde is the Schiff fuchsin test. The reagent is a solution of a dye (fuchsin) which has been decolorized by the addition of sulfur dioxide. The resulting solution gives a blue-violet color in the presence of any aldehyde. However, except in the case of formaldehyde, the color is discharged when acid is added. This test can be adapted for use with methyl alcohol. For example, its presence in ethyl alcohol can be shown by oxidizing the mixture to the aldehydes and carrying out the test. If the blue-violet color remains after acidification, it signifies that methanol was present in the original sample.

Large quantities of formaldehyde are consumed in the manufacture of synthetic polymers, particularly those obtained with phenol and with urea.

**Acetaldehyde.** Acetaldehyde is an important industrial raw material. It is obtained both by the catalytic dehydrogenation of ethyl alcohol (page 80) and by the hydration of acetylene.



Acetaldehyde, in contact with an acid at low temperatures, undergoes trimerization to give paraldehyde, which is used as a hypnotic.



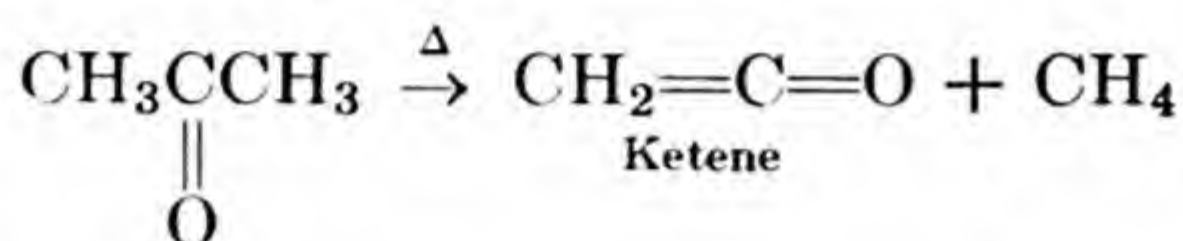
If it is warmed with acid, paraldehyde is reconverted to acetaldehyde.



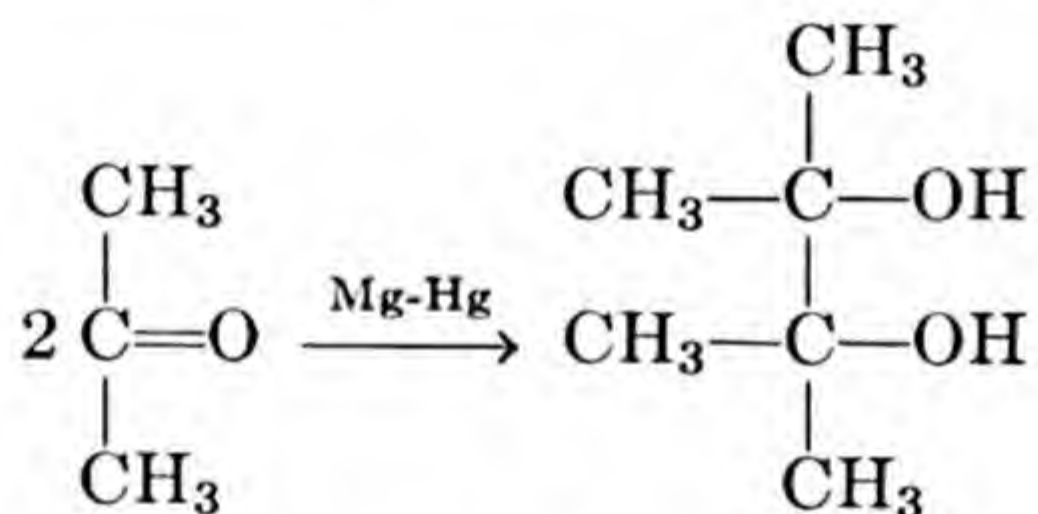
Since paraldehyde is a liquid and acetaldehyde, a gas, this supplies a convenient source of acetaldehyde in the laboratory.

**Acetone.** Acetone, the simplest ketone, is a good solvent for many organic substances and on this account finds considerable application in the lacquer industry. The largest supply of acetone is made by the dehydrogenation of isopropyl alcohol.

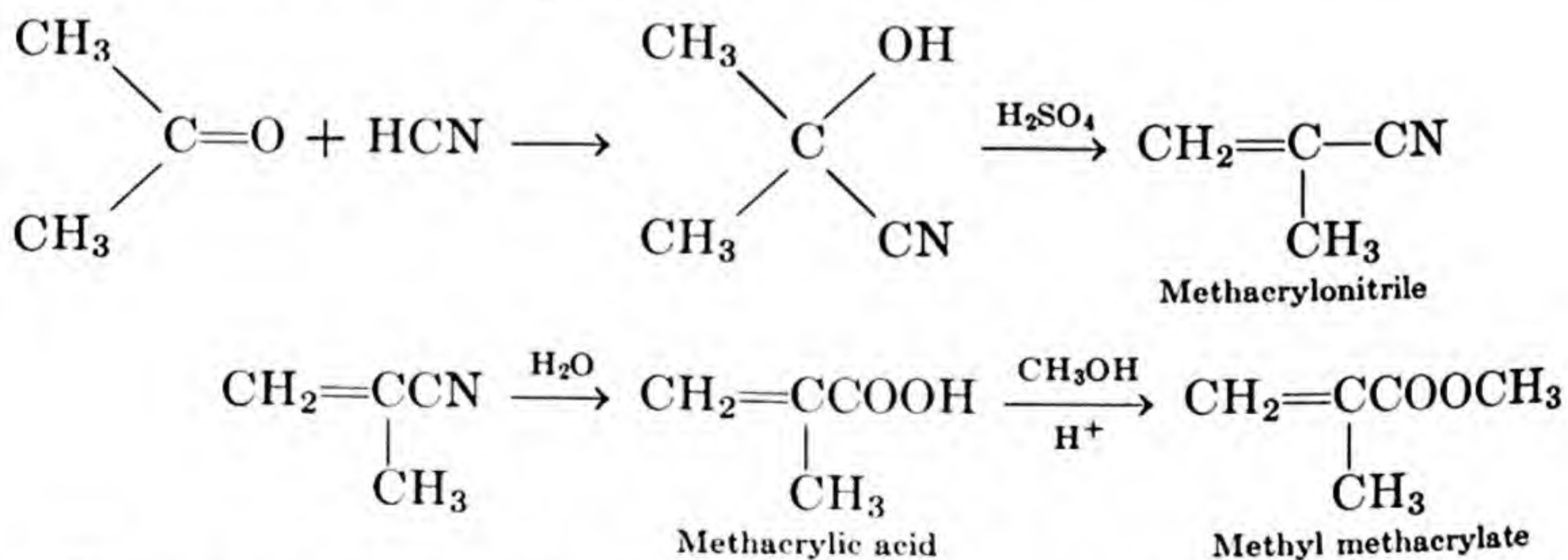
The most important chemical outlet for acetone is the manufacture of ketene, a very reactive substance from which acetic anhydride and a variety of other useful products are made.



An interesting reaction of acetone, shared by many other ketones, is its bimolecular reduction to pinacol by means of magnesium amalgam.



Acetone is also a raw material in the preparation of other valuable substances. Thus in the presence of alkali it condenses to yield diacetone alcohol, a high-boiling solvent (p. 90). Acetone cyanohydrin can be made to produce various derivatives of methacrylic acid used in the manufacture of polymers.



The ester can be obtained without isolation of the intermediates; it is produced from the cyanohydrin with sulfuric acid and the alcohol. Polymethyl methacrylate is a plastic of useful and interesting properties (p. 120).

## ► NATURALLY OCCURRING CARBONYL COMPOUNDS

Certain aldehydes and ketones have been isolated from plant extracts, examples of which are given in the table. Citral and citronellal, it is to be noted, obey the isoprene rule.

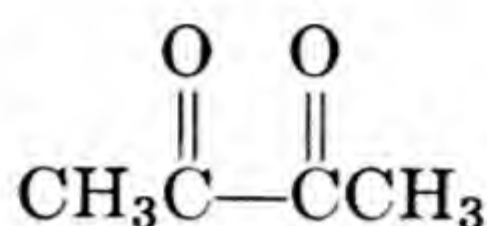
Naturally Occurring Aldehydes and Ketones

Name	Structure	Occurrence
Citral	$\begin{array}{c} \text{CH}_3\text{C}=\text{CHCH}_2\text{CH}_2\text{C}=\text{CHC} \begin{array}{l} \text{H} \\ \text{O} \end{array} \\   \qquad \qquad   \\ \text{CH}_3 \qquad \text{CH}_3 \end{array}$	Lemon and orange oils
Citronellal	$\begin{array}{c} \text{CH}_3\text{C}=\text{CHCH}_2\text{CH}_2\text{CHCH}_2\text{C} \begin{array}{l} \text{H} \\ \text{O} \end{array} \\   \qquad \qquad   \\ \text{CH}_3 \qquad \text{CH}_3 \end{array}$	Lemon and citronella oils
Cinnamaldehyde	$\text{C}_6\text{H}_5\text{CH}=\text{CHC} \begin{array}{l} \text{H} \\ \text{O} \end{array}$	Cinnamon
Vanillin	$\begin{array}{c} \text{HC} \text{---} \text{C}_6\text{H}_4 \text{---} \text{C} \begin{array}{l} \text{H} \\ \text{O} \end{array} \\   \\ \text{CH}_3\text{O} \end{array}$	Vanilla bean
2-Heptanone	$\begin{array}{c} \text{O} \\    \\ \text{CH}_3\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \end{array}$	Clove oil
Jasmone	$\begin{array}{c} \text{CH}_3 \\   \\ \text{C} \\ / \quad \backslash \\ \text{CH}_2 \quad \text{CCH}_2\text{CH}=\text{CHCH}_2\text{CH}_3 \\   \qquad   \\ \text{CH}_2 \text{---} \text{C}=\text{O} \end{array}$	Jasmine

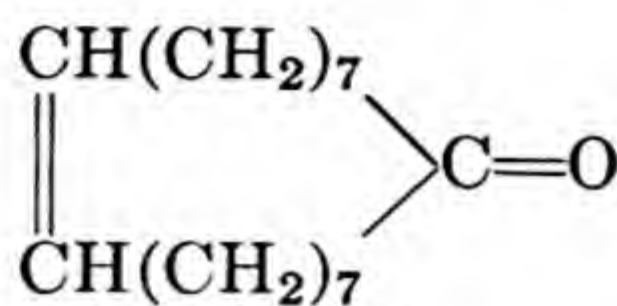
Certain animal products of interest are aldehydes and ketones. For example, biacetyl is partly responsible for the odor, flavor, and color of butter. Two other animal products are civetone and muscone, from the African civet cat and the Asiatic musk deer, respectively. These are cyclic ketones with unusually large rings. Such substances are valuable in perfumery; a synthetic product, cyclo-



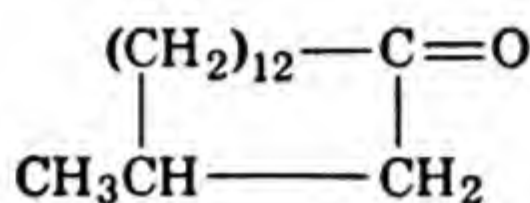
pentadecanone (sold under the name of Exaltone) is also used for this purpose.



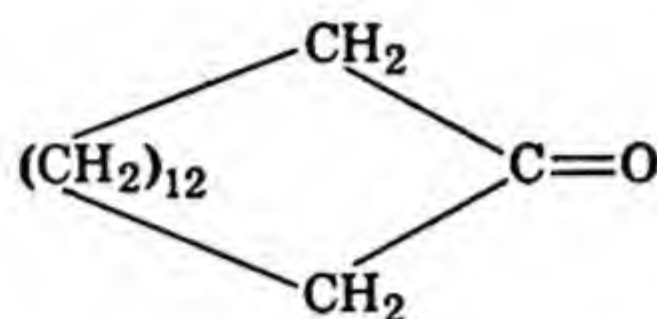
Biacetyl



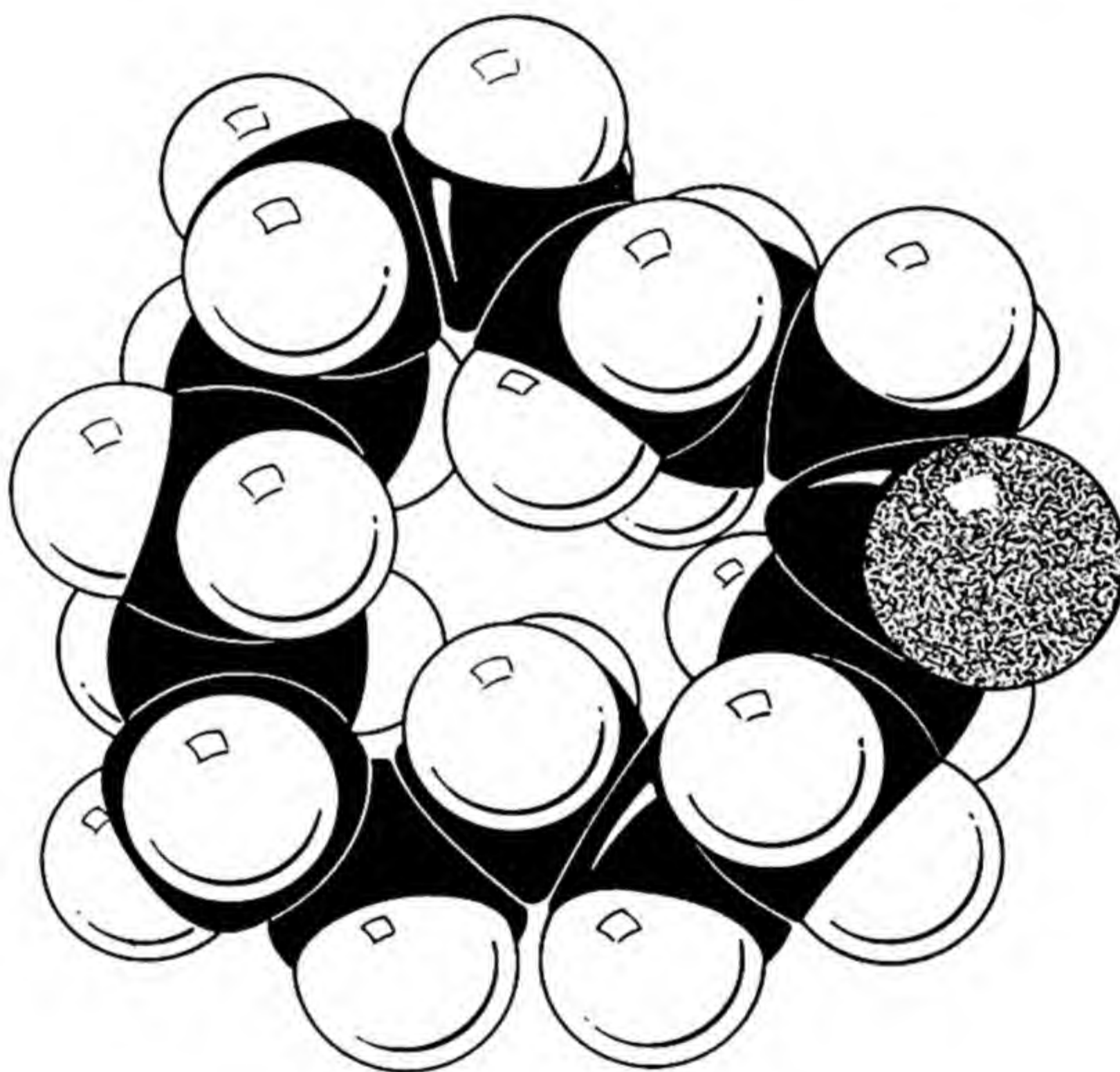
Civetone



Muscone



Cyclopentadecanone



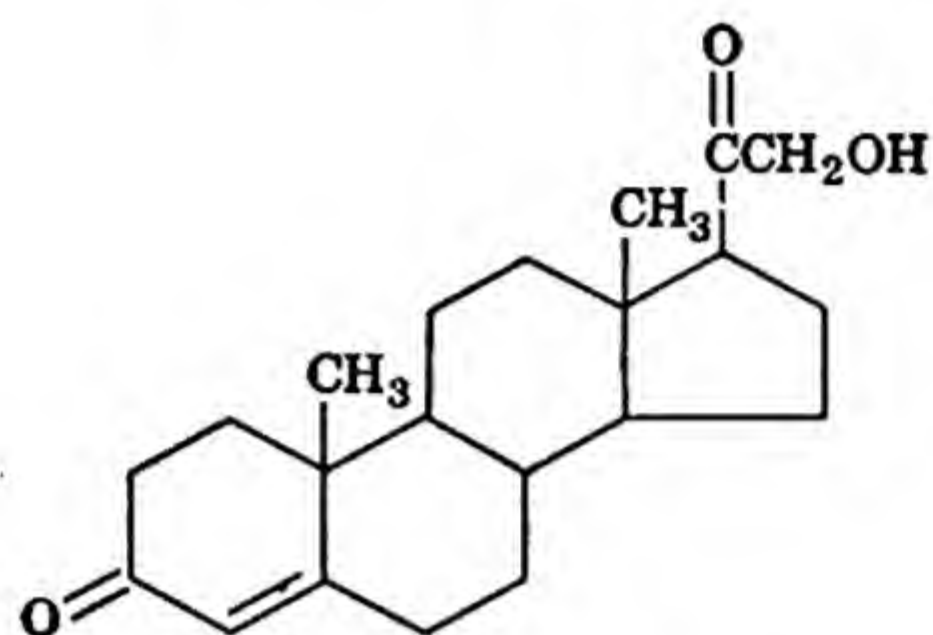
*Cyclopentadecanone*

In the early history of organic chemistry it was believed that only five- and six-membered rings could exist. It is now known that large rings occur in nature, and though they are difficult to synthesize large ring compounds are stable substances.

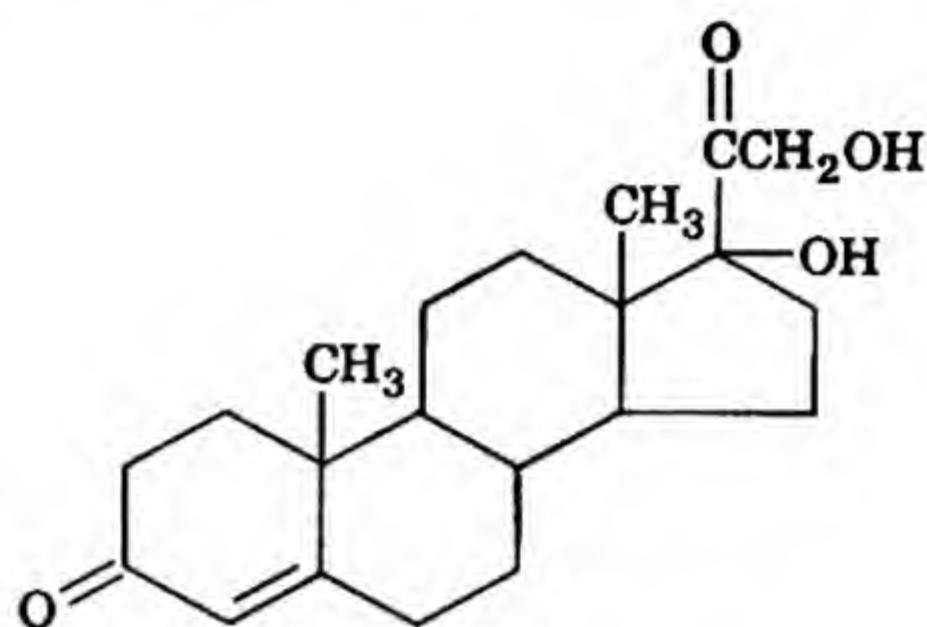
The hormones of the adrenal cortex and two of the sex hormones are ketones. In general, hormones are manufactured by the body in various ductless glands, such as the pituitary, thyroid, pancreas, and gonads. They have the power to control specific features of body

metabolism and growth. Little is known of their method of exercising this control.

The structures of some adrenal cortex hormones follow. Like the sterols (Chapter 7), they have the steroid ring system.

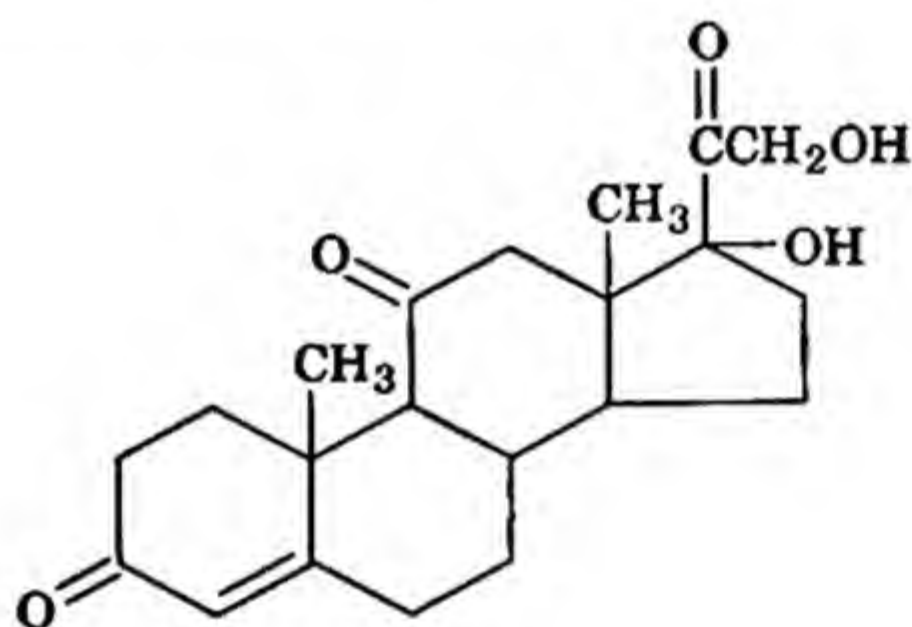


Desoxycorticosterone

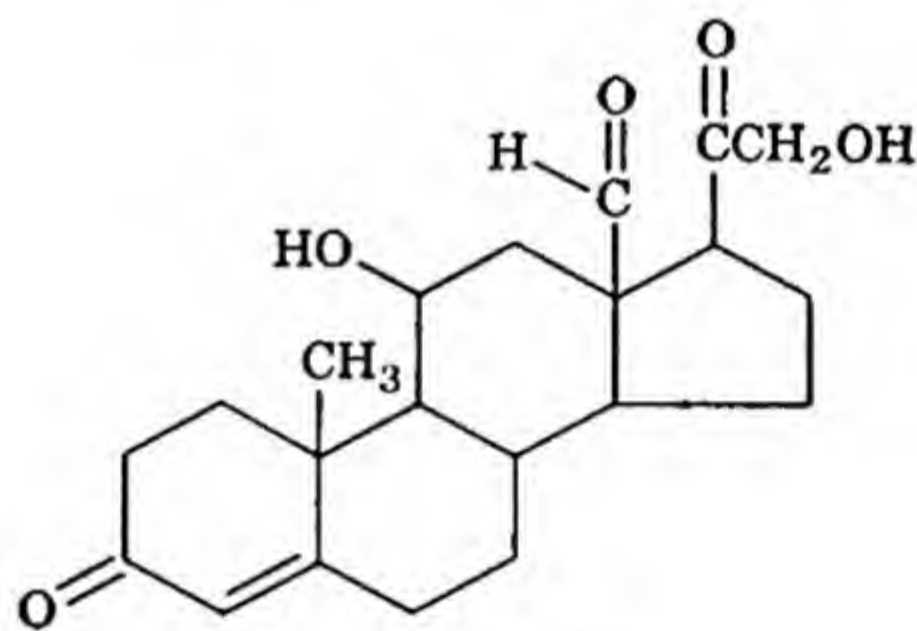


17-Hydroxydesoxycorticosterone

The cortical hormones are concerned with water and electrolyte balances and with carbohydrate metabolism. Aldosterone is the most potent mineral-controlling hormone. Atrophy of the adrenals results

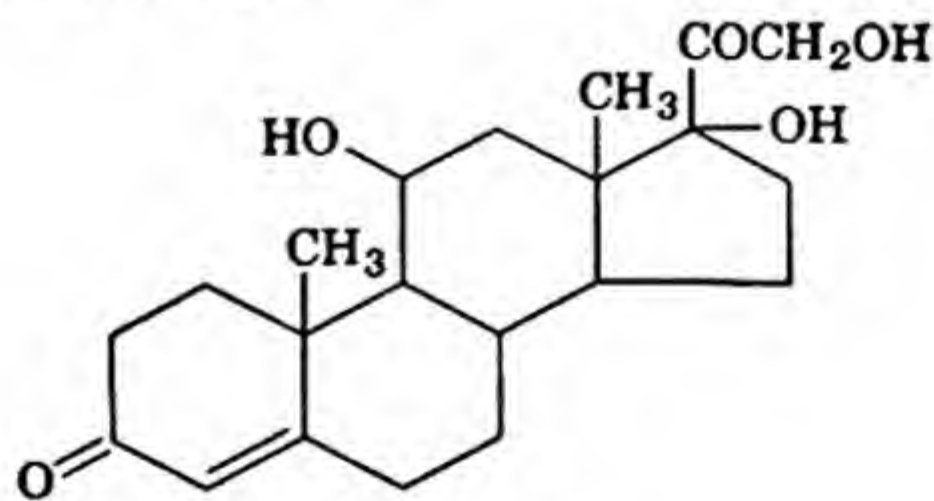


Cortisone



Aldosterone

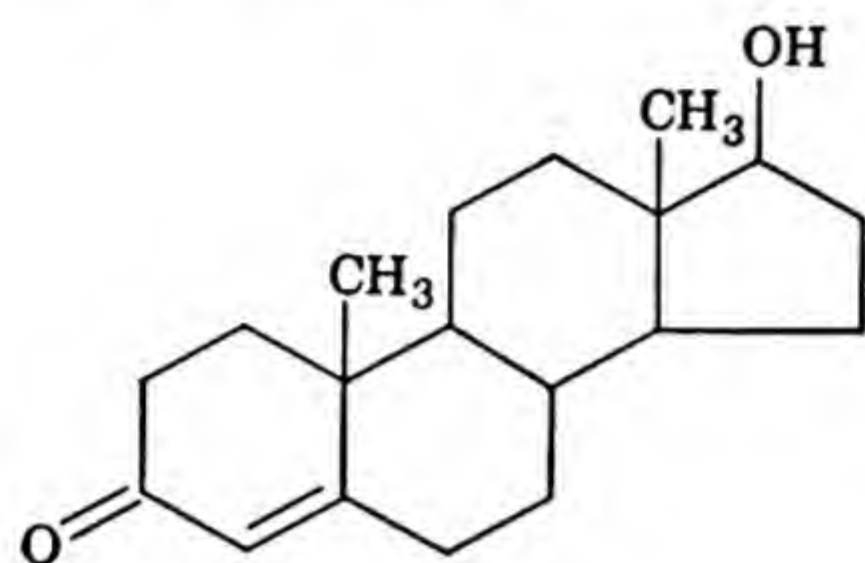
in Addison's disease, which is ultimately fatal, but regular administration of adrenocortical extracts prolongs life. Gastrointestinal disturbances, muscular weakness, and a peculiar bronzing of the skin are the effects of Addison's disease. Cortisone has shown remarkable powers in alleviating rheumatoid arthritis, and hydrocortisone is very effective as an anti-inflammatory agent which finds much use in the treatment of dermal allergies.



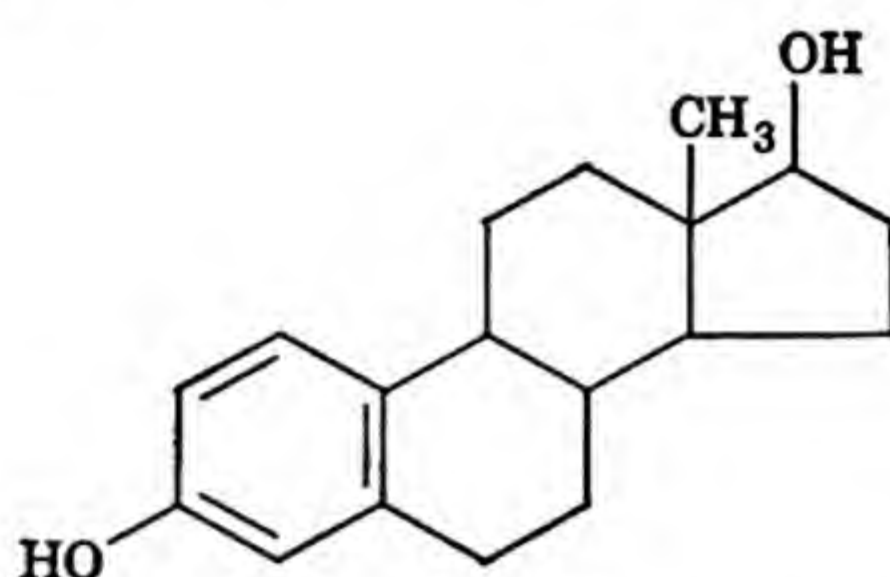
Hydrocortisone



The male sex hormone, which is secreted by the testes, is testosterone. It is concerned with the development of the male reproductive organs and secondary sex characteristics and appears to be involved in general health and well-being.

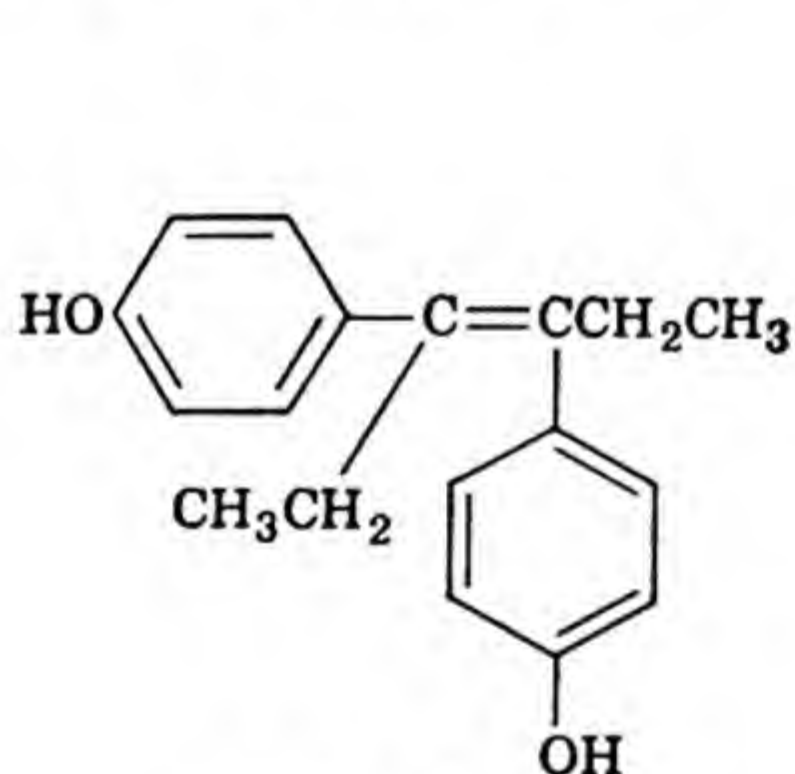


Testosterone

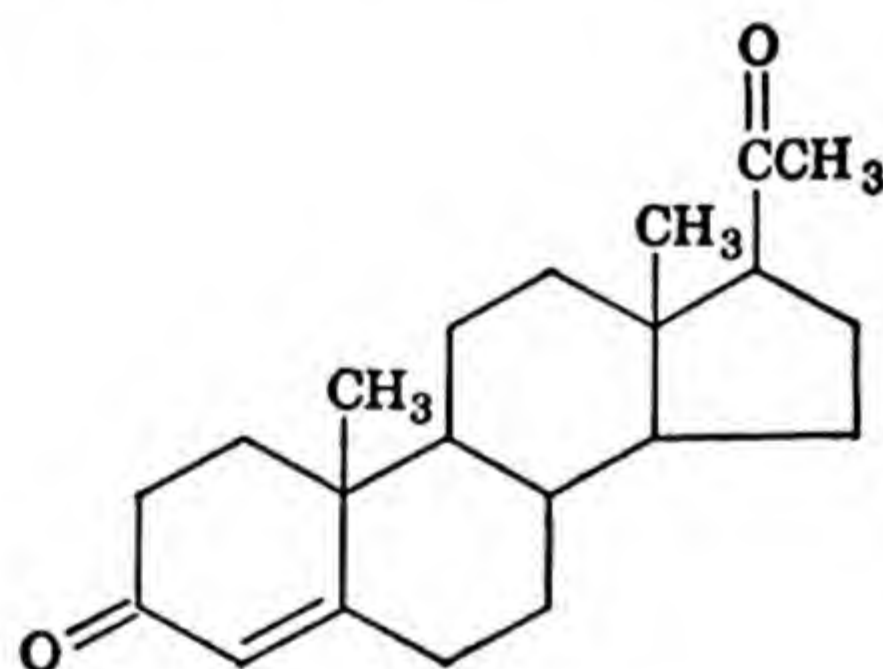


Estradiol

There are at least two types of female sex hormone. Estradiol is secreted by the ovaries. Like testosterone in men, estradiol is concerned with the development of secondary sex characteristics and the general health and well-being of women. It is also involved in menstruation. Certain synthetic substances, such as stilbestrol, have physiological properties similar to those of estradiol. Progesterone is produced by the corpus luteum and is responsible for the maintenance of pregnancy. It aids in developing the walls of the uterus for the nurture of the fetus. Following conception, the placenta becomes an important hormone-producing gland.



Stilbestrol



Progesterone

Male and female sex hormones are produced by both sexes. The relative amounts of the two types are different, however.

## ► QUESTIONS

1. Rutgers 612, 2-ethyl-1,3-hexanediol, is an insect repellent. Show by equations how it can be obtained from *n*-butyraldehyde.

2. Suppose that an unknown is one of the following: hexanal, 2-hexanone, or 3-hexanone. Show how you could test to determine the identity of the unknown.

3. Complete the following:

- (a) 2-Pentanone + NaOCl →
- (b) Acetone + HCN →
- (c) Acetaldehyde + Benedict's reagent →
- (d) Cyclohexanone + NaHSO<sub>3</sub> →
- (e) Benzophenone + H<sub>2</sub>NOH →
- (f) 2,2-Dimethylpropanal + NaOH →

4. Illustrate the following reactions:

- (a) Cannizzaro reaction with *p*-tolualdehyde
- (b) Aldol condensation with phenylacetaldehyde
- (c) Oxime formation with methyl ethyl ketone
- (d) Acetal formation with benzaldehyde
- (e) Haloform reaction with acetone

5. If a mixture of acetaldehyde and propionaldehyde is treated with alkali, four possible aldol condensations can occur. Write the equations.

6. Bottles of benzaldehyde which have been allowed to stand for some time gradually accumulate a white solid. What is the probable structure of this substance? Explain how it is produced.

7. Show the structures of the products which would be obtained in the following Friedel-Crafts reactions:

- (a) Chlorobenzene + acetyl chloride
- (b) Benzene + ClCCl (phosgene)



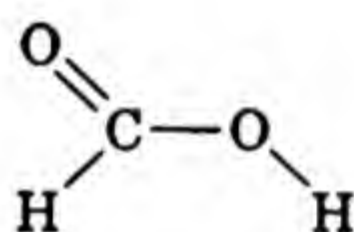
- (c) *p*-Xylene + acetic anhydride
- (d) Anisole + C<sub>6</sub>H<sub>5</sub>COCl (benzoyl chloride)

8. Write the structures of the compounds that would be formed if the products of question 7 were treated with methylmagnesium iodide, CH<sub>3</sub>MgI, and the adducts hydrolyzed.

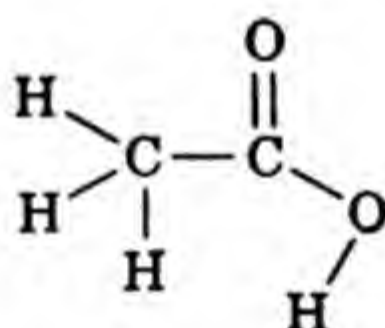


## chapter 10

# Carboxylic acids and their derivatives



Formic acid



Acetic acid

Formic and acetic acids are the first two members of the homologous series of the fatty acids. Formic acid, as is frequently the case with the first member of a series, is more reactive and has some properties not possessed by the other members.

The carboxyl group,  $\begin{array}{c} \text{O} \\ \parallel \\ -\text{C} \\ | \\ \text{OH} \end{array}$ , is the functional group of the car-

boxylic acids. When the carboxyl group is attached to a saturated aliphatic group the compound is said to be a fatty acid because such compounds are obtained when fats are hydrolyzed. Since they were known before systematic nomenclature was devised, these acids have commonly used trivial names.

Of the compounds given in the table, formic, propionic, and valeric acids occur only rarely in nature. The others are found in small or

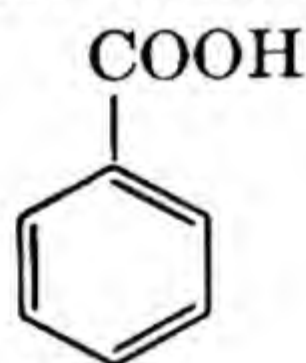
### Fatty Acids

Name	Formula	B.P.	M.P.	Occurrence
Formic acid	HCOOH	101	8	Ants, bees
Acetic	CH <sub>3</sub> COOH	118	17	Vinegar
Propionic	CH <sub>3</sub> CH <sub>2</sub> COOH	141	-22	
Butyric	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> COOH	163	-5	Butter
Valeric	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> COOH	186	-35	Valerian plant
Caproic	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>4</sub> COOH	205	-2	Butter
Caprylic	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>6</sub> COOH	237	16	Butter
Capric	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>8</sub> COOH	269	31	Butter
Lauric	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>10</sub> COOH		44	Palm oil
Myristic	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>12</sub> COOH		58	Nutmeg fat
Palmitic	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>14</sub> COOH		63	All fats and oils
Stearic	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>16</sub> COOH		69	All fats and oils

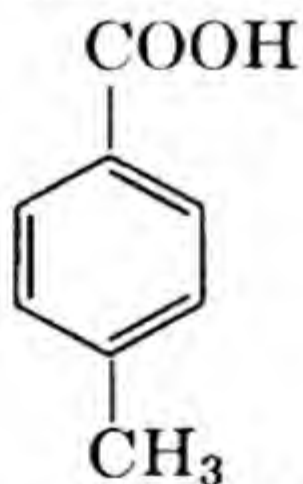
large amounts in many fats and vegetable oils, in the form of esters with glycerol (Chapter 11). It is interesting that the most abundant naturally occurring acids have straight chains and an even number of carbon atoms. Apparently the mechanism by which the organism synthesizes the acids leads to this result. Both branched-chain and odd-numbered acids occur naturally, but in smaller amounts.

Though all of the lower fatty acids have odors, those of four through ten carbon atoms are especially obnoxious. The odors associated with fats, such as butter and lard which have become rancid, with goats, and with certain cheeses are caused by these compounds.

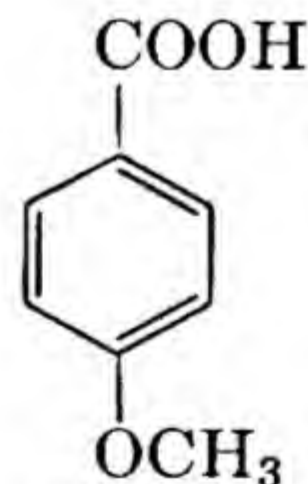
It is fortunate that the properties of the carboxyl group are very nearly the same, irrespective of the type of group to which it is attached. Thus the properties of the aromatic and heterocyclic acids can be studied simultaneously with those of the fatty acids. Examples of these acids are shown below.



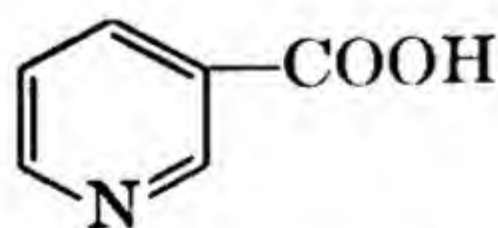
Benzoic acid



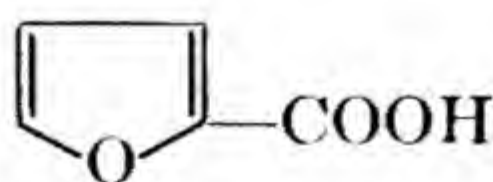
*p*-Toluic acid



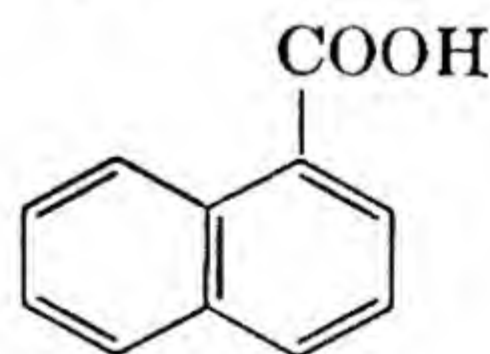
*p*-Anisic acid



Nicotinic acid



Furoic acid



$\alpha$ -Naphthoic acid

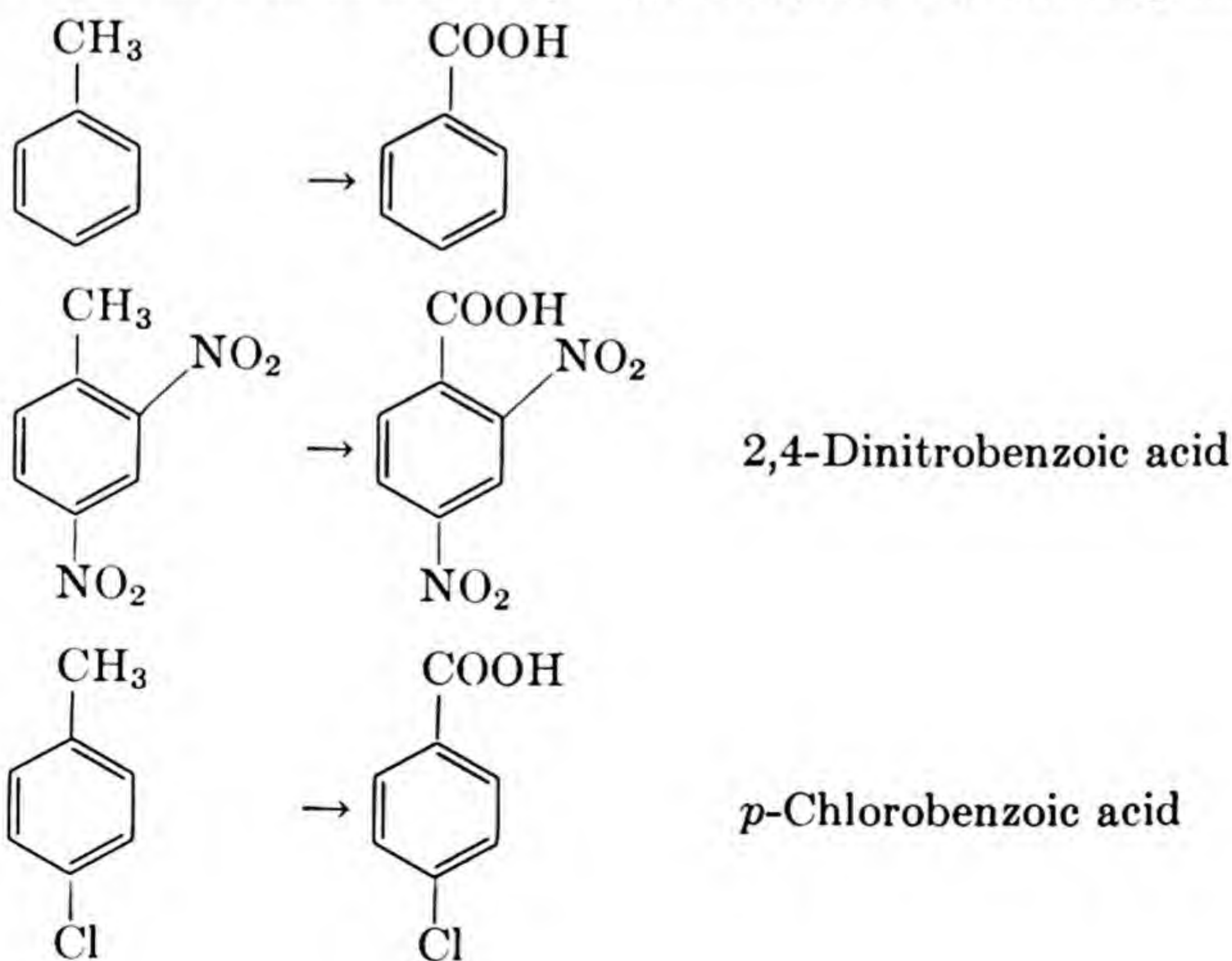


Except for the lower fatty acids, carboxylic acids are not appreciably soluble in water. Since their alkali metal salts are soluble, the acids can be dissolved in aqueous sodium hydroxide or sodium carbonate solutions and can be reprecipitated therefrom by acidification. This property is useful in separating the acids from neutral or basic impurities. The carboxylic acids are weak; that is, they are very little ionized in solution. Acetic acid, for example, is less than 0.01% ionized in 5% aqueous solution.

### ► SOURCES OF ACIDS

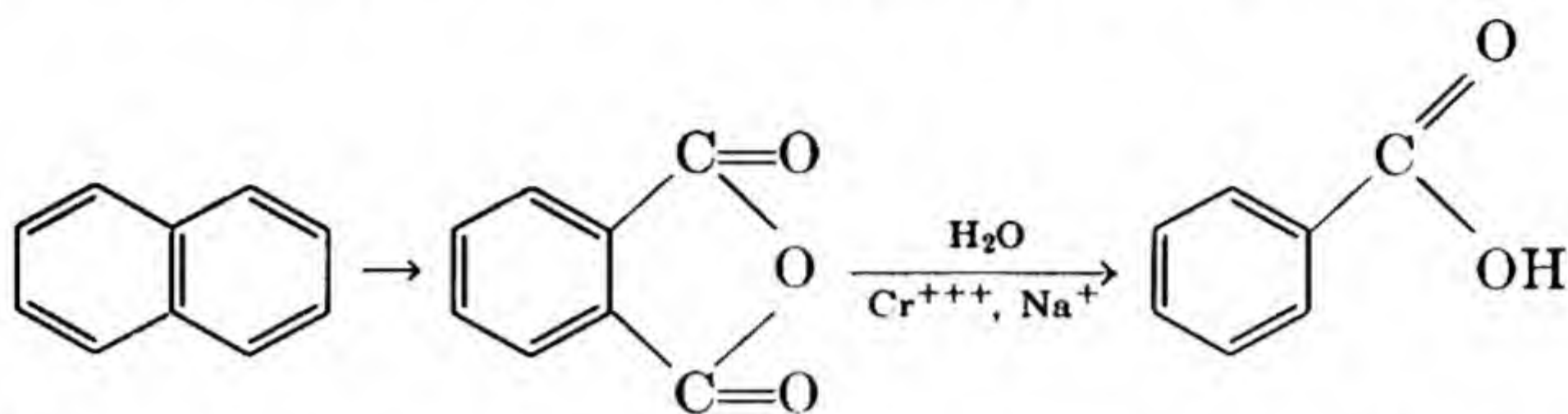
The fats and oils provide the most economical source of high-molecular-weight fatty acids. The mixtures of acids obtained from most fats and oils by hydrolysis are exceptionally complex, and to obtain pure acids difficult purification procedures are necessary. Some fats and oils, however, produce a preponderance of a particular fatty acid in hydrolysis and thus provide a convenient source for that acid. An example is nutmeg fat, from which myristic acid is obtained.

A method of preparation widely used for aliphatic acids consists in the oxidation of primary alcohols or aldehydes. Acetic acid is obtained commercially from acetaldehyde by oxidation with the oxygen of the air in the presence of cobalt or manganese acetate. Aromatic acids can be made by oxidation, but the starting material

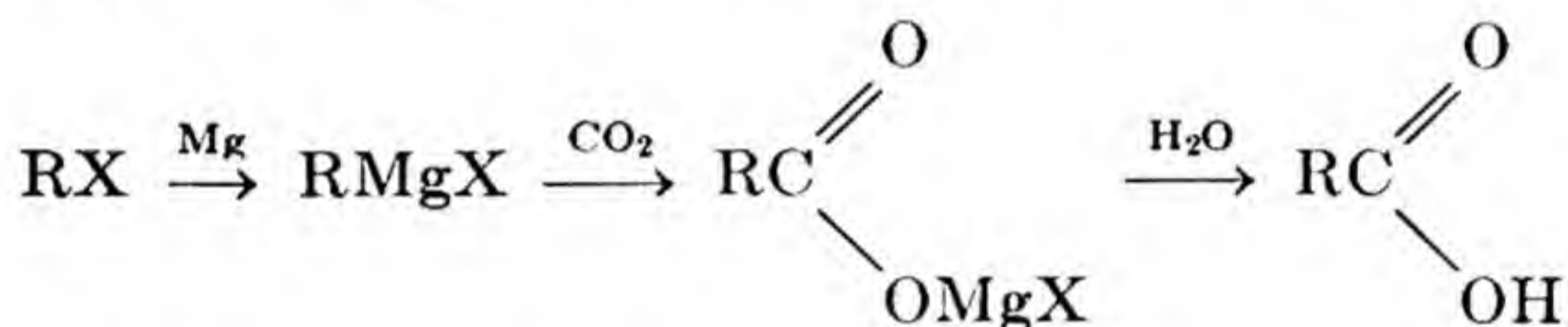


is usually an alkylated benzene derivative so that strong oxidizing agents are needed. This reaction succeeds with aromatic compounds because of the great resistance to oxidation of the benzene nucleus.

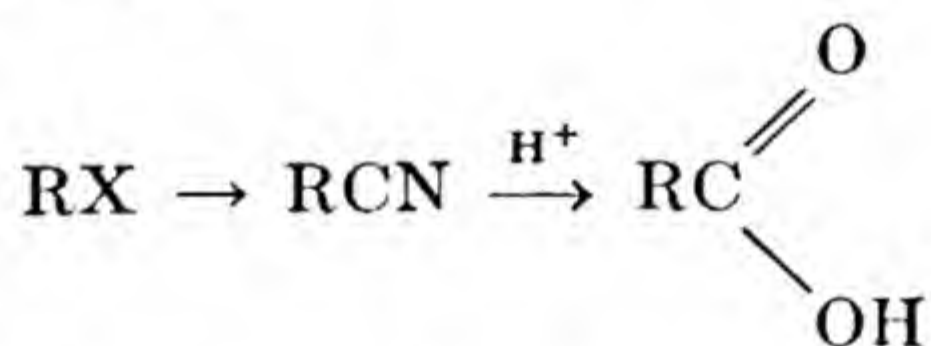
Benzoic acid is made industrially by a modification of this process. Naphthalene is oxidized catalytically to phthalic anhydride, which upon treatment with water and a catalyst produces benzoic acid.



Halogen derivatives of hydrocarbons provide good laboratory sources for acids. In the Grignard synthesis the halide is converted into the Grignard reagent, which is treated with carbon dioxide.

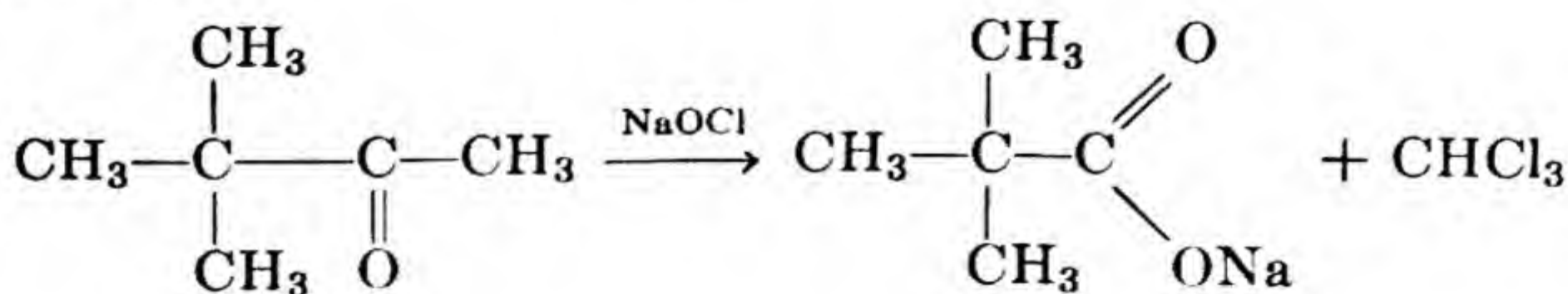


This method is suitable for the preparation of many aliphatic and aromatic acids. Halogen derivatives may also be converted into acids by way of the nitriles.



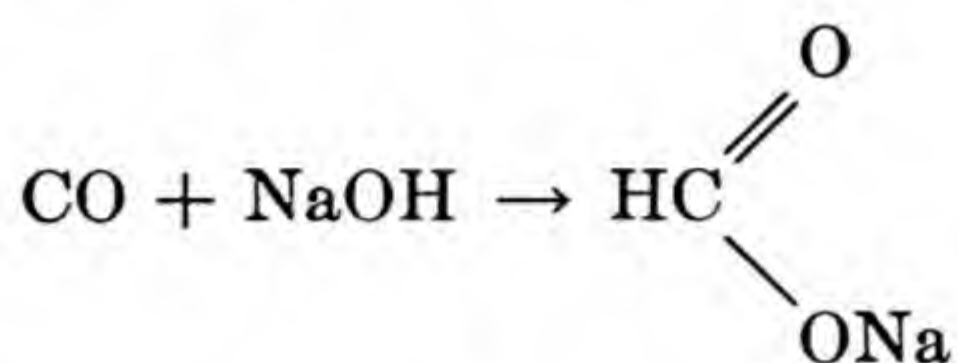
With alkyl halides, the preparation of the nitrile usually succeeds with sodium cyanide if R is primary. With aromatic halides, the conversion of the halide to the nitrile is effected by the action of cuprous cyanide in the presence of pyridine.

Another method of making acids, occasionally resorted to in the laboratory, is the haloform reaction. In Chapter 9 this method was shown for senecioic acid. It is also useful for pivalic (trimethylacetic) acid.

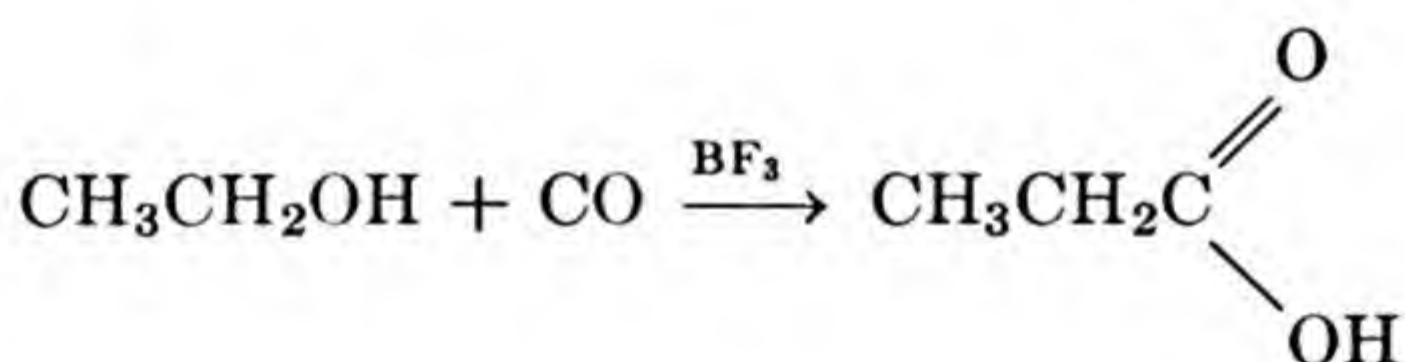
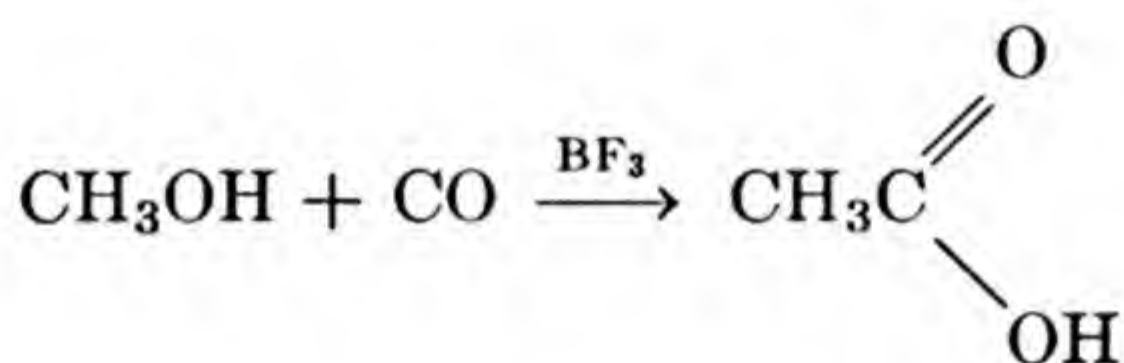
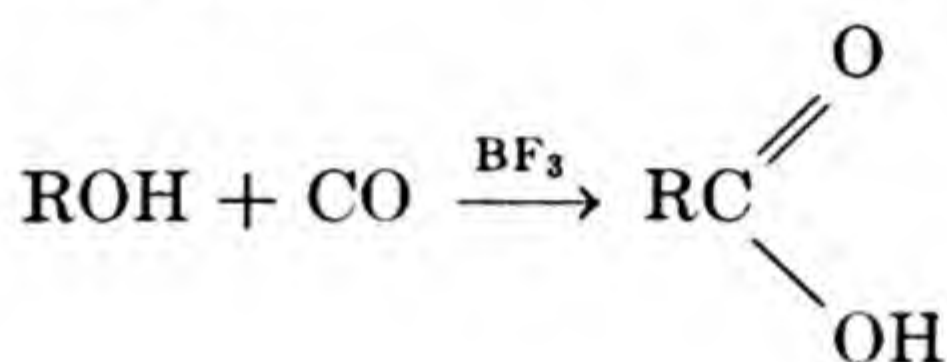




Carbon monoxide is a raw material for the industrial preparation of acids. If it is heated under pressure with sodium hydroxide, carbon monoxide yields sodium formate, and formic acid can be obtained from the salt by acidification.



Acetic and propionic acids are made from carbon monoxide and the alcohol of one fewer carbon atom; the reaction is carried out under pressure and with a catalyst.

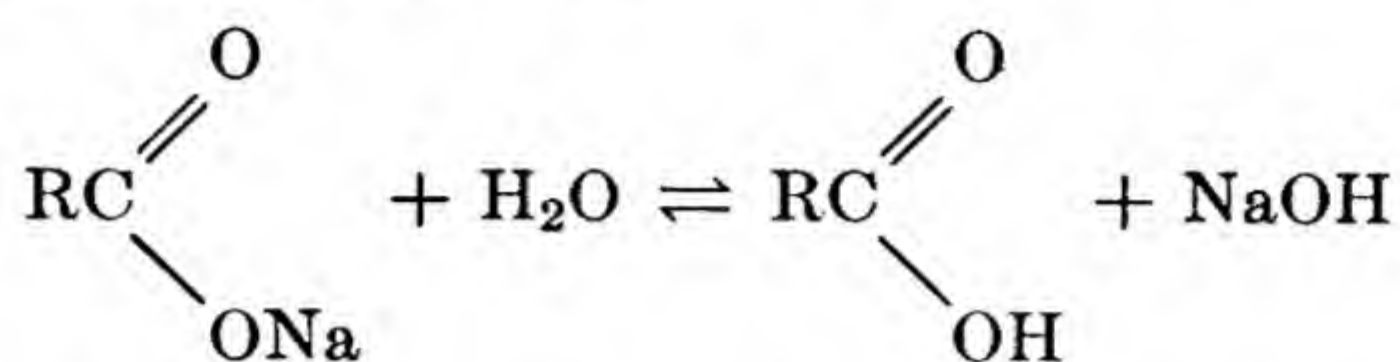


## ► ACID DERIVATIVES

The carboxyl group readily undergoes modifications which give rise to several classes of acid derivatives. The most important of these are salts, acid chlorides, anhydrides, esters, amides, and nitriles. All can be hydrolyzed to regenerate the parent acid; the conditions necessary, however, differ with the type of derivative.

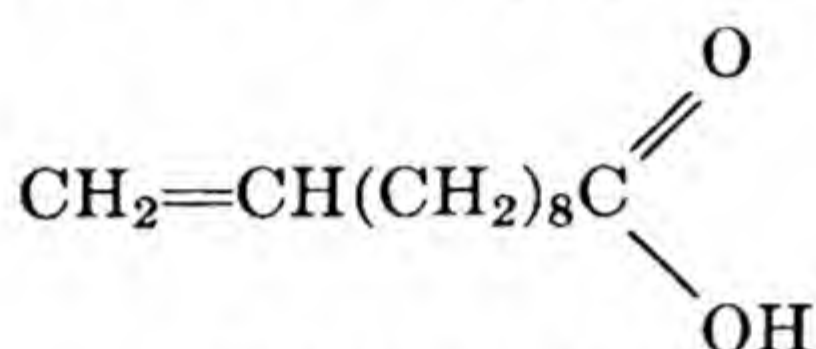
**Salts.** Organic acids react with hydroxides, carbonates, or oxides to give salts which have many of the properties of inorganic salts. They have very high melting points and are little soluble in organic solvents. Many of them are soluble in water. Carboxylic acids are only slightly ionized in water, and their salts are therefore hydrolyzed to a considerable extent in that solvent. It follows that the solutions

of alkali metal salts are alkaline to litmus, since the hydroxides of these elements are strong bases.



Sodium propionate is used as a mold inhibitor in bread, and the sodium and calcium salts of propionic and caprylic acids find application in the treatment of fungus infections of the skin, such as athlete's foot.

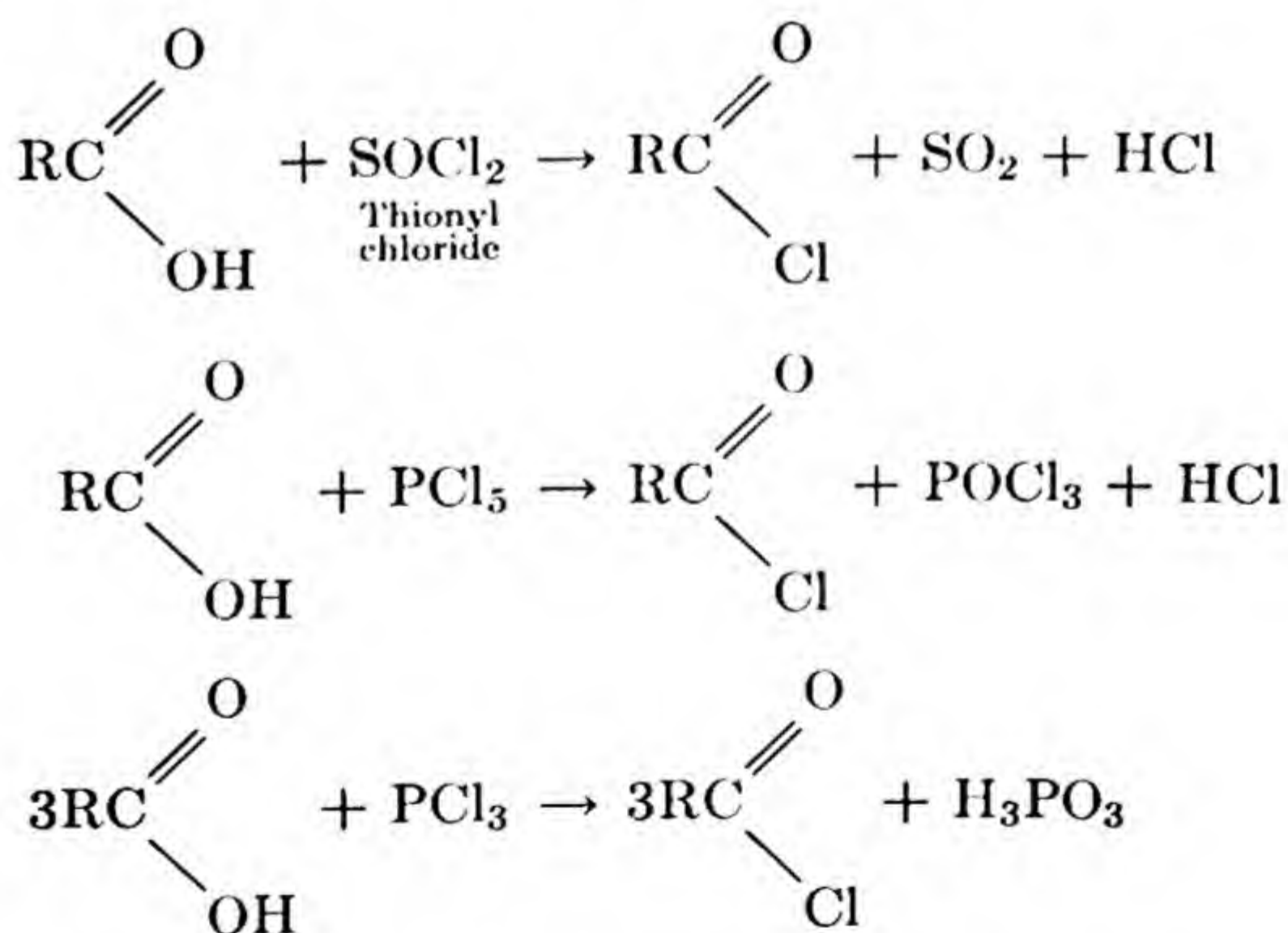
Undecylenic acid has also been employed for this purpose.



Undecylenic acid

The soaps, which are salts of long-chain fatty acids, are dealt with in Chapter 11.

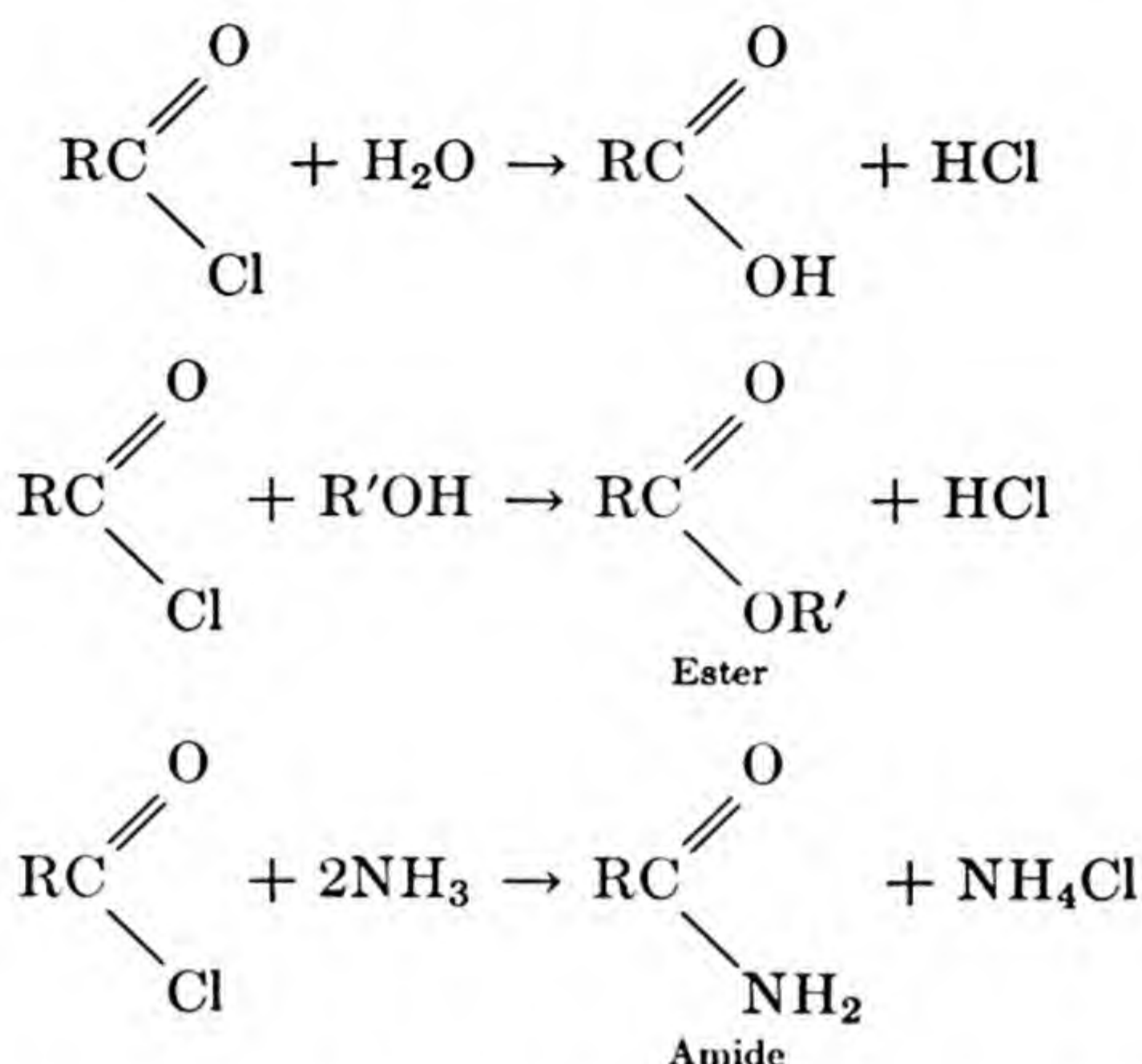
**Acid Chlorides.** Acids react with thionyl chloride, phosphorus pentachloride, or phosphorus trichloride to give acid chlorides in which the hydroxyl portion of the acid group is replaced by a chlorine atom.



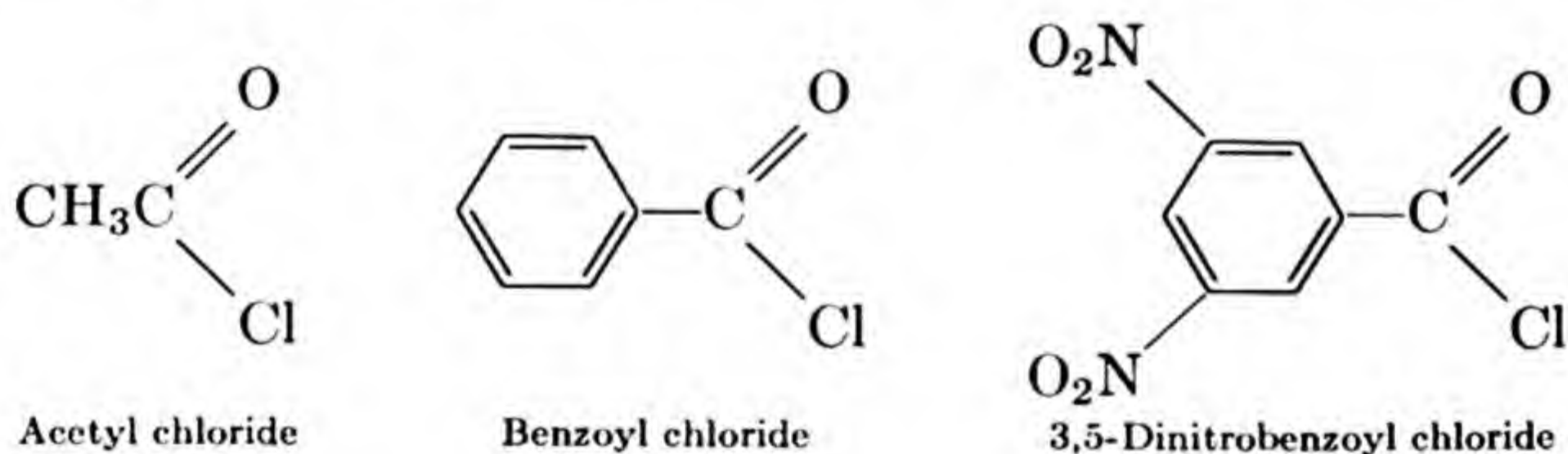
The acid chlorides are very reactive substances. In company with other acid derivatives, they are hydrolyzed to their parent acids.



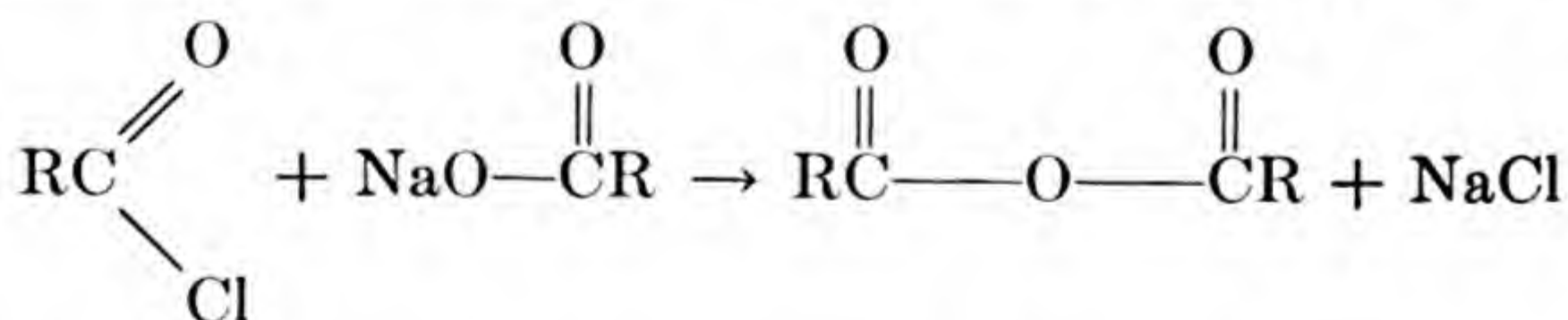
They also react readily with alcohols and with ammonia to yield esters and amides. It should be noted that in all three cases reaction occurs so that the chlorine of the acid chloride is lost as hydrogen chloride.



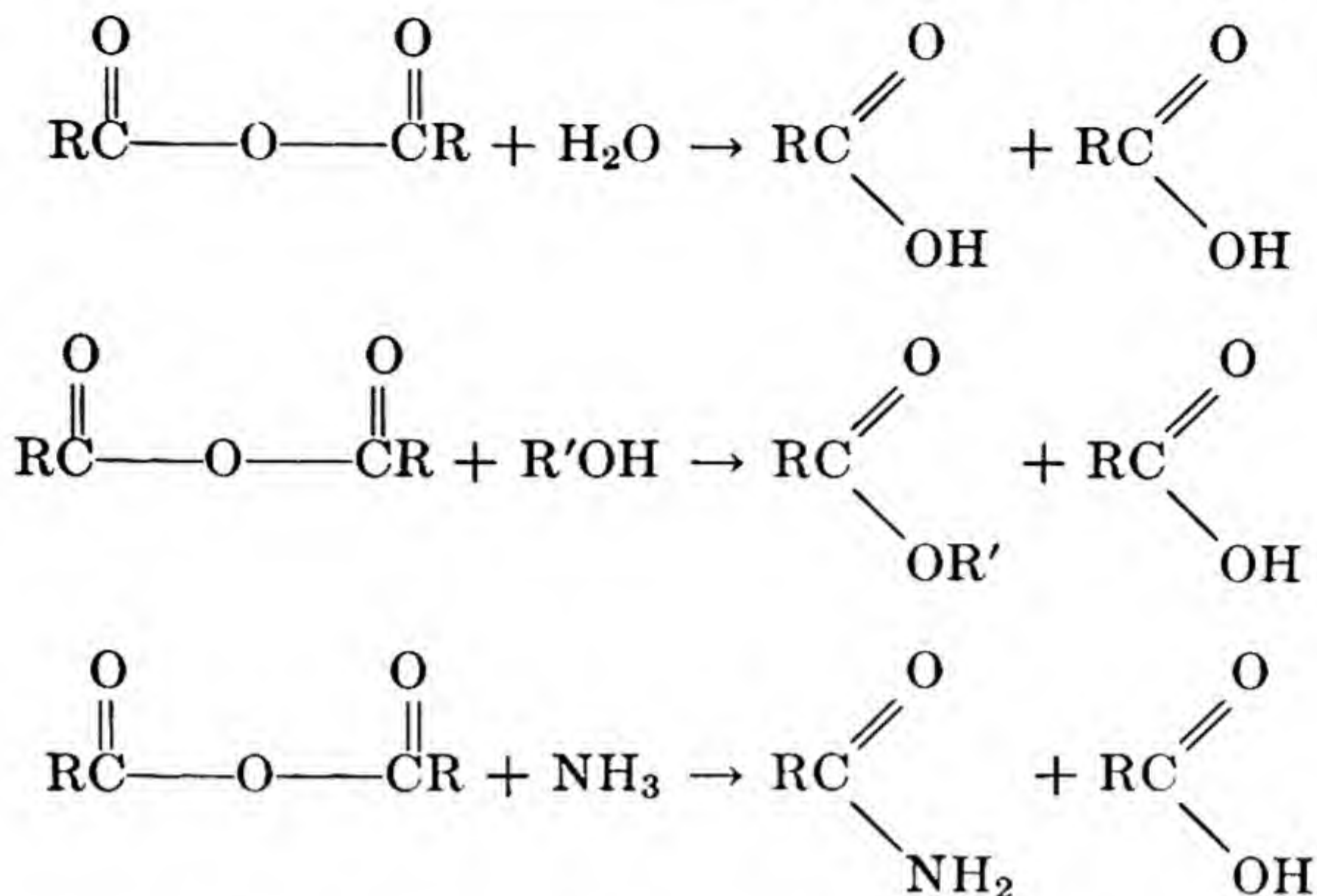
The acid chlorides are named by reference to the acids; the suffix “-ic” is replaced by “-yl” and the word “acid,” by “chloride.”



Acid chlorides react with salts of organic acids to give anhydrides.

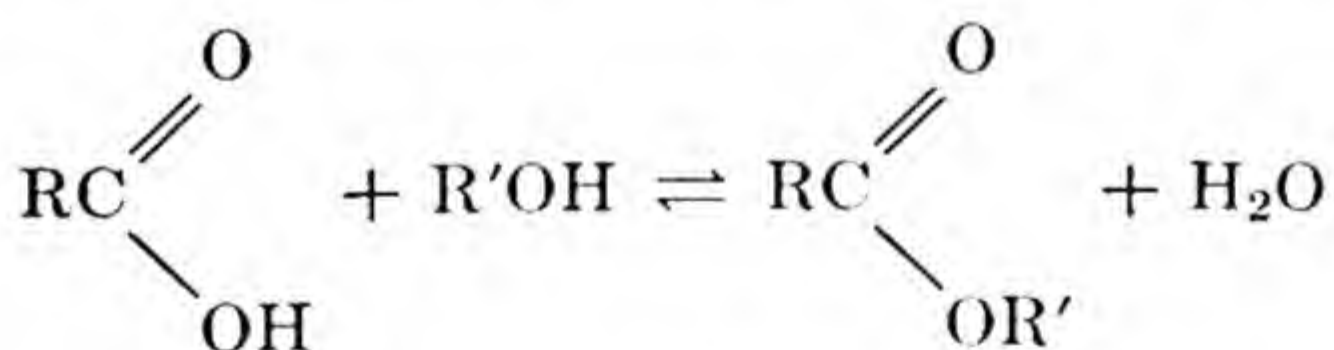


**Acid Anhydrides.** Acid anhydrides in which the groups are unlike are called mixed anhydrides. It is particularly helpful to recognize that acid chlorides are mixed anhydrides of organic and hydrochloric acids. It follows that anhydrides and acid chlorides undergo very similar reactions. Thus water, alcohols, and ammonia convert the anhydrides to acids, esters, and amides, respectively.

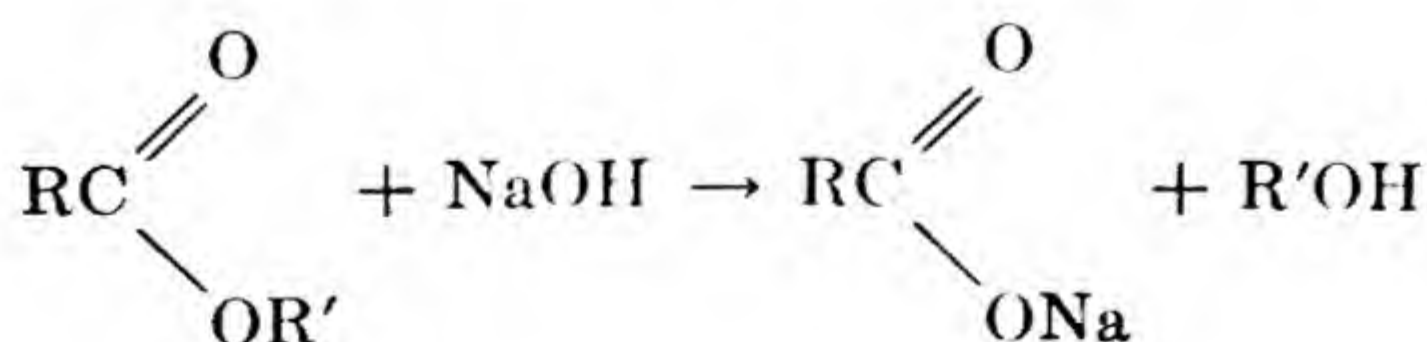


In these reactions a molecule of organic acid is produced in every case. In the corresponding reactions of acid chlorides hydrogen chloride is formed in each instance. Because of their great reactivity the acid chlorides are widely employed in preparative work. A few anhydrides, such as acetic anhydride, which are commercially available, are used in a similar way.

**Esters.** When an alcohol and an acid react, an ester is produced. The reaction is reversible and is catalyzed by strong acids.



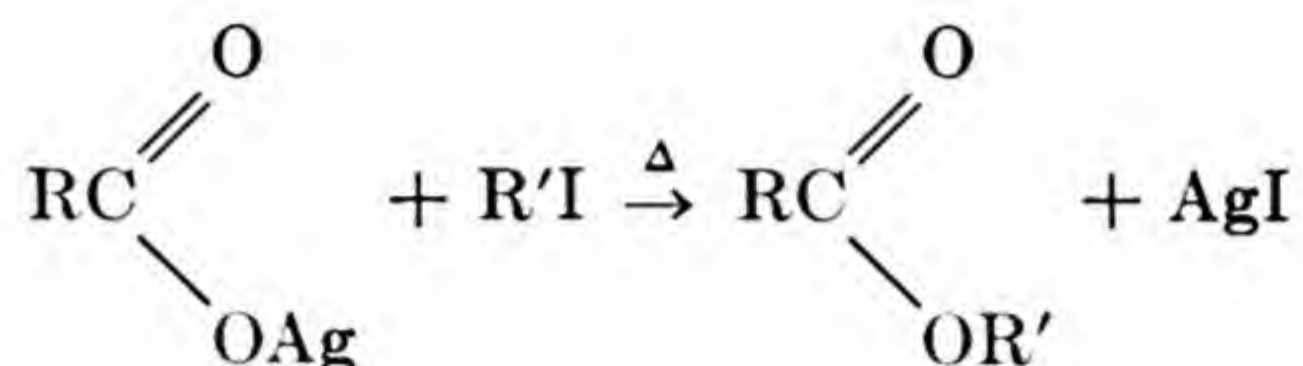
With one mole each of acid and alcohol, equilibrium is attained when about  $\frac{2}{3}$  mole of ester is present. Under these conditions a maximum yield of approximately 67% can be realized. An excess of alcohol or acid improves the yield of ester according to the law of mass action. The forward reaction is called *esterification*. The reverse reaction—the hydrolysis of esters—can be made complete if carried out in the presence of a base which converts the acid to a salt.



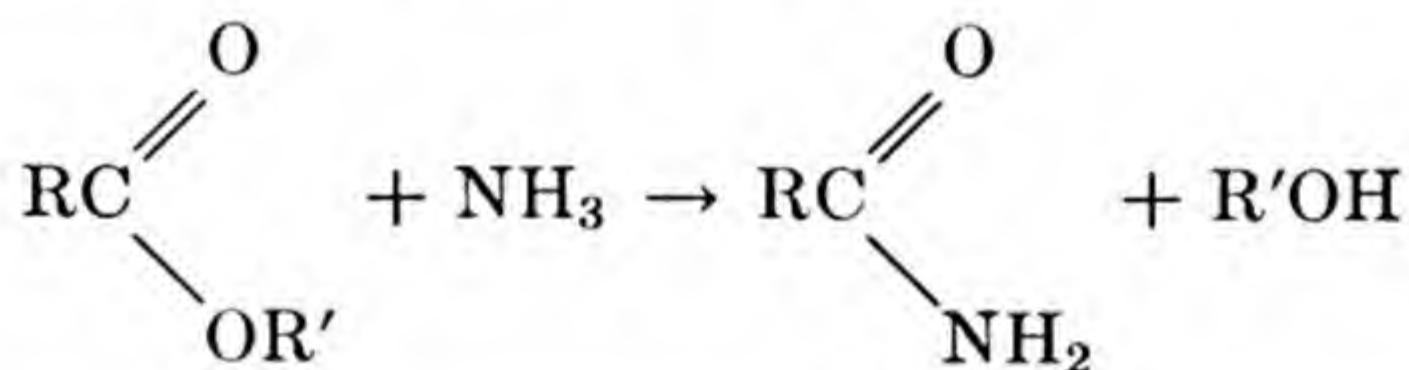


This type of reaction is called *saponification*; the term derives from the fact that the manufacture of soaps from fats or oils is the alkaline hydrolysis of an ester, but it has come to be applied to the alkaline hydrolysis of any ester.

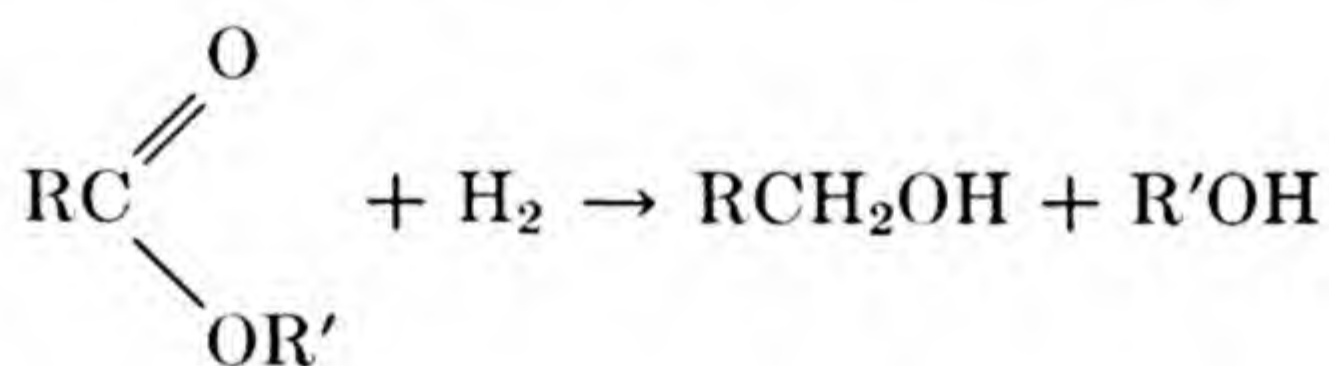
Esters can also be obtained by the reaction of acid chlorides or anhydrides with alcohols, as stated earlier. They are occasionally prepared by heating the salt of an acid with an alkyl halide.



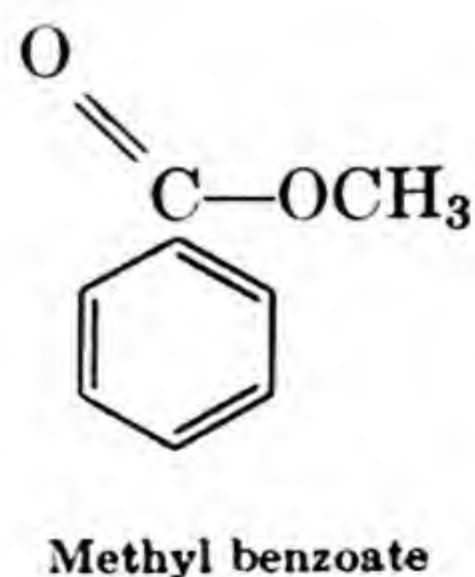
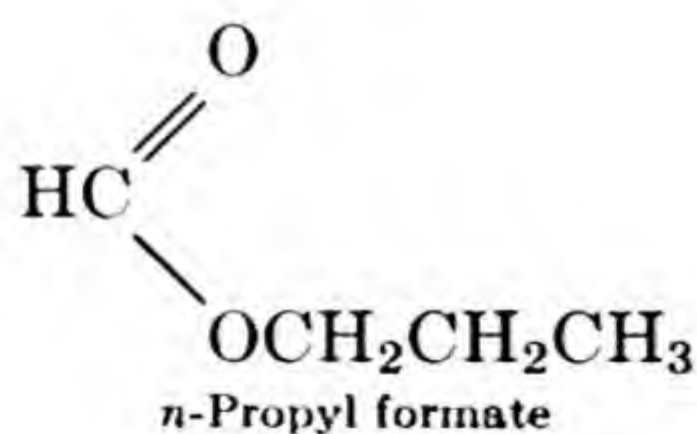
Like the acid chlorides and anhydrides, esters react with ammonia to yield amides, but the reaction is slower.

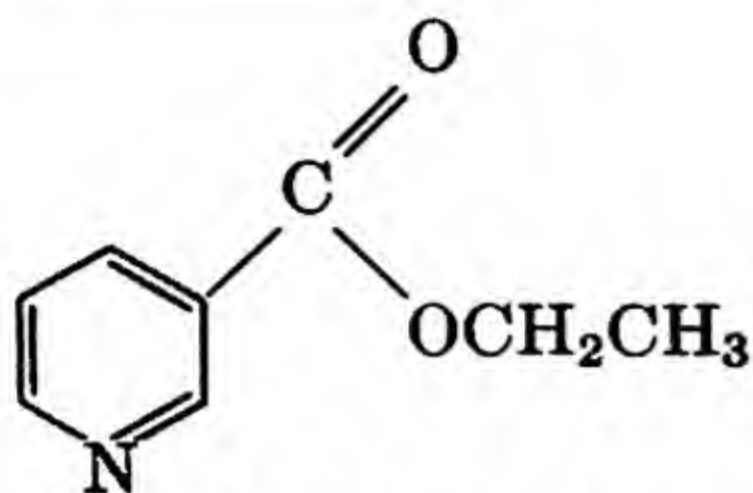


Esters are cleaved by hydrogen at high temperature and pressure and in the presence of a copper-chromium oxide catalyst to give two alcohol molecules. It has been found that lithium aluminum hydride,  $\text{LiAlH}_4$ , will accomplish this reduction also.

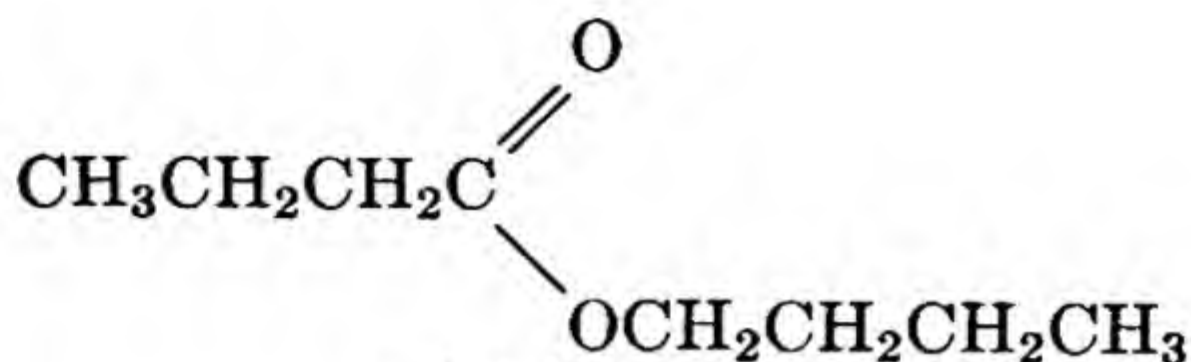


Esters are named by first stating the name of the group in the alcohol portion of the ester and following with the name of the acid portion in which “-ic” is changed to “-ate.” The formulas of a few esters with their names are given below.

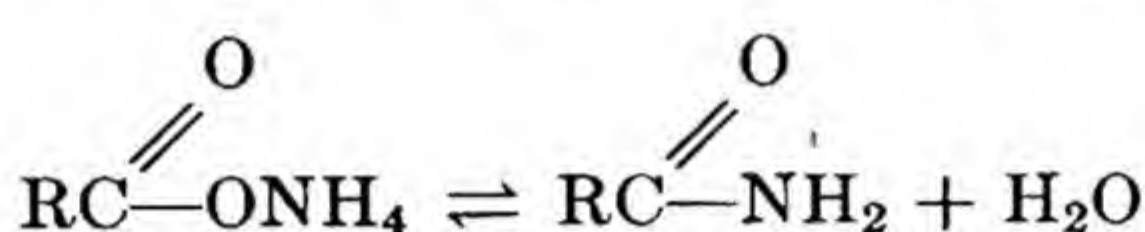




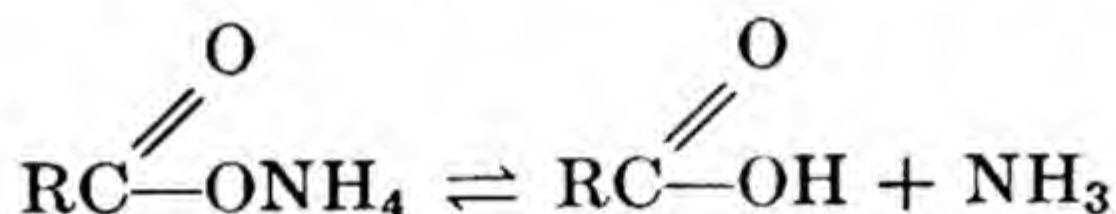
Ethyl nicotinate


*n*-Butyl-*n*-butyrate

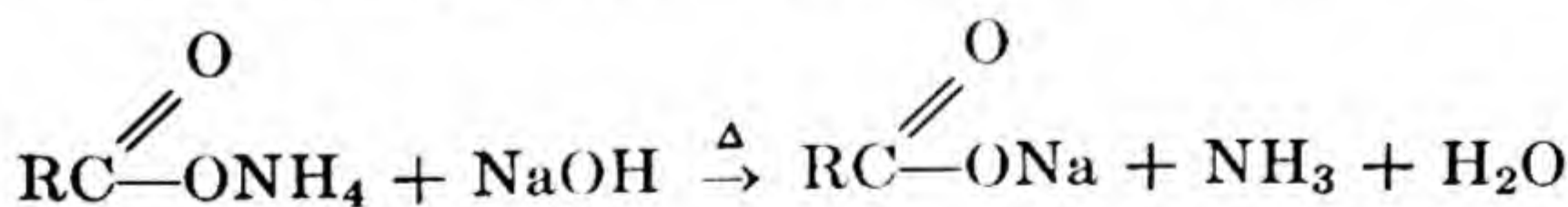
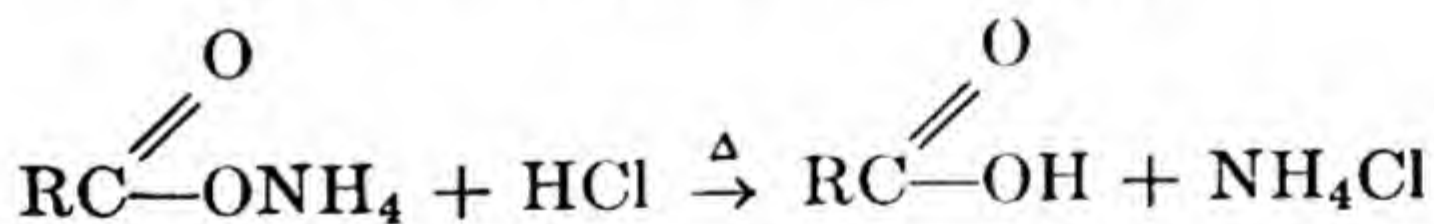
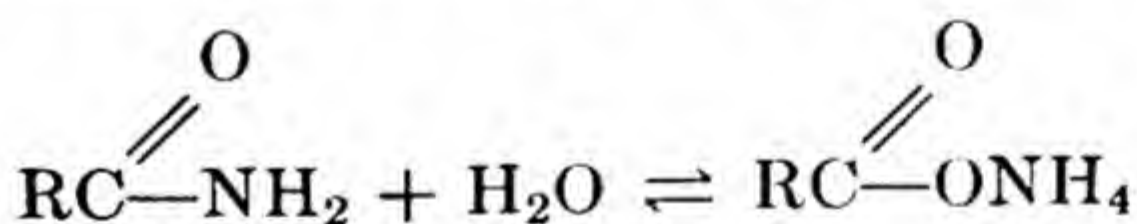
**Amides.** The amides,  $\text{RC}(=\text{O})\text{NH}_2$ , can be obtained by treatment of acid chlorides, anhydrides, or esters with ammonia. They can also be prepared from ammonium salts by heating. It is desirable to add a



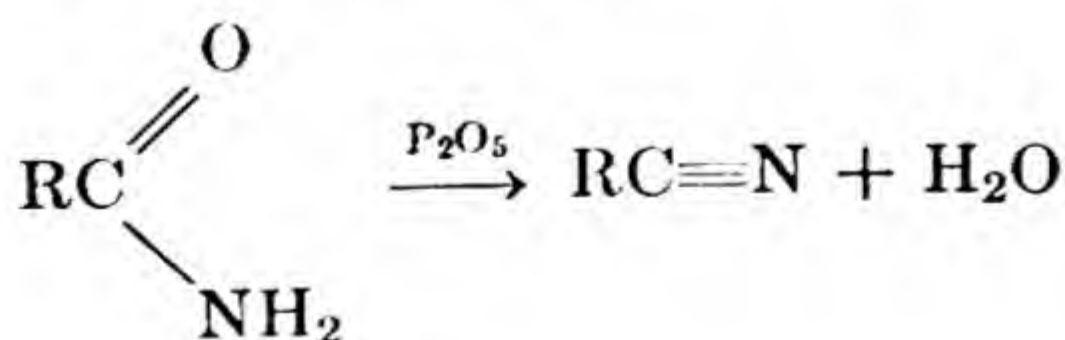
large amount of ammonia or of the acid to the reaction mixture in order to avoid the decomposition of the salt to ammonia and the acid.



All unsubstituted amides except formamide are solids. Like other acid derivatives, they can be converted to the parent acids by hydrolysis, but hot acid or alkali may be required.

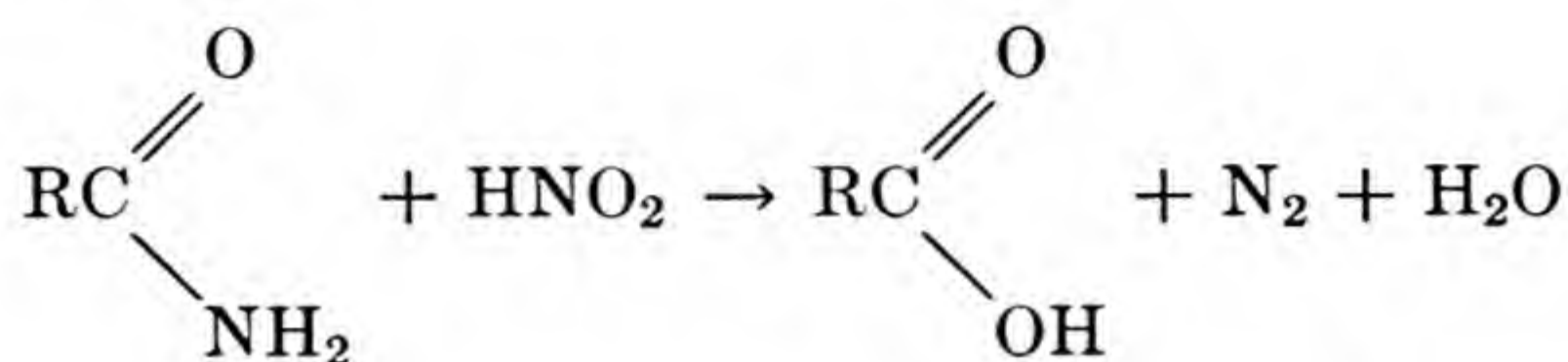


Dehydrating agents such as phosphorus pentoxide cause amides to lose water and form nitriles (cyanides).

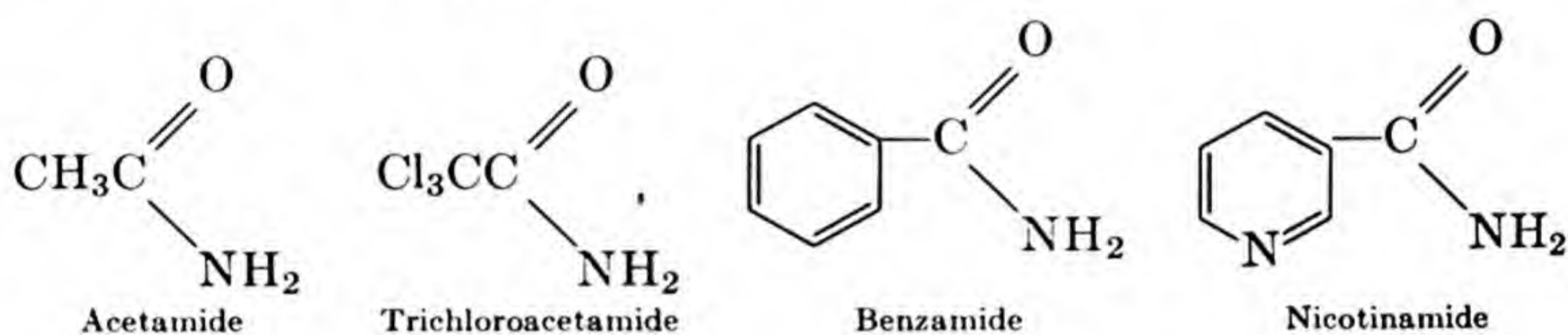




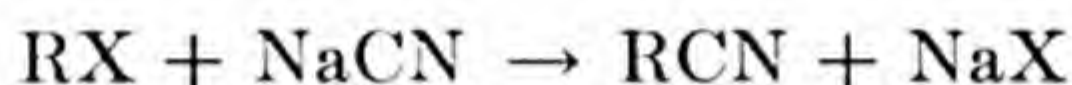
Amides also react with nitrous acid to give the carboxylic acids; nitrogen is evolved.



Amides are named by reference to the parent acid. Inspection of the formulas will reveal the method used:

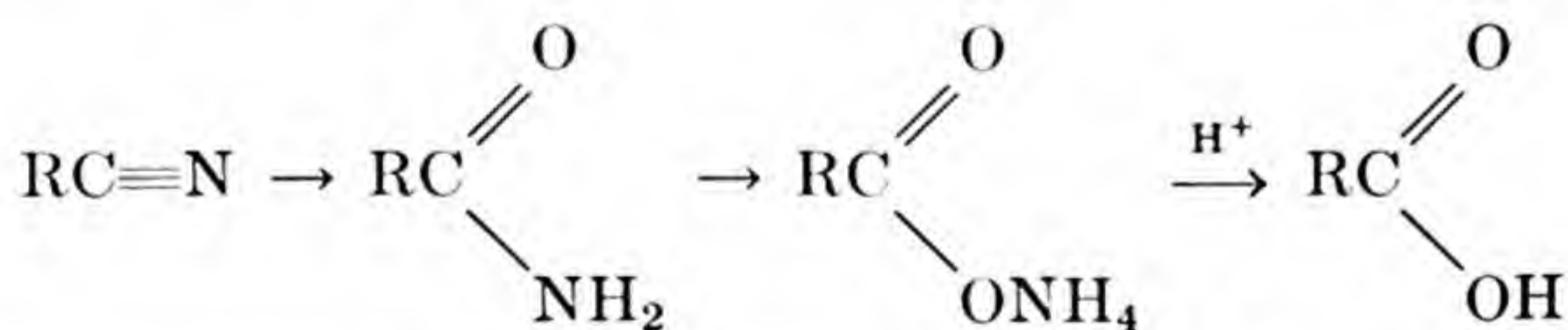


**Nitriles.** As mentioned in the preceding section, nitriles are prepared by the reaction of dehydrating agents with amides. They are also obtained by heating alkyl halides with an inorganic cyanide.



The isocyanide RNC is formed as a by-product in this reaction. The use of sodium cyanide fails with most aromatic halides, as stated earlier, but cuprous cyanide is successful in some cases.

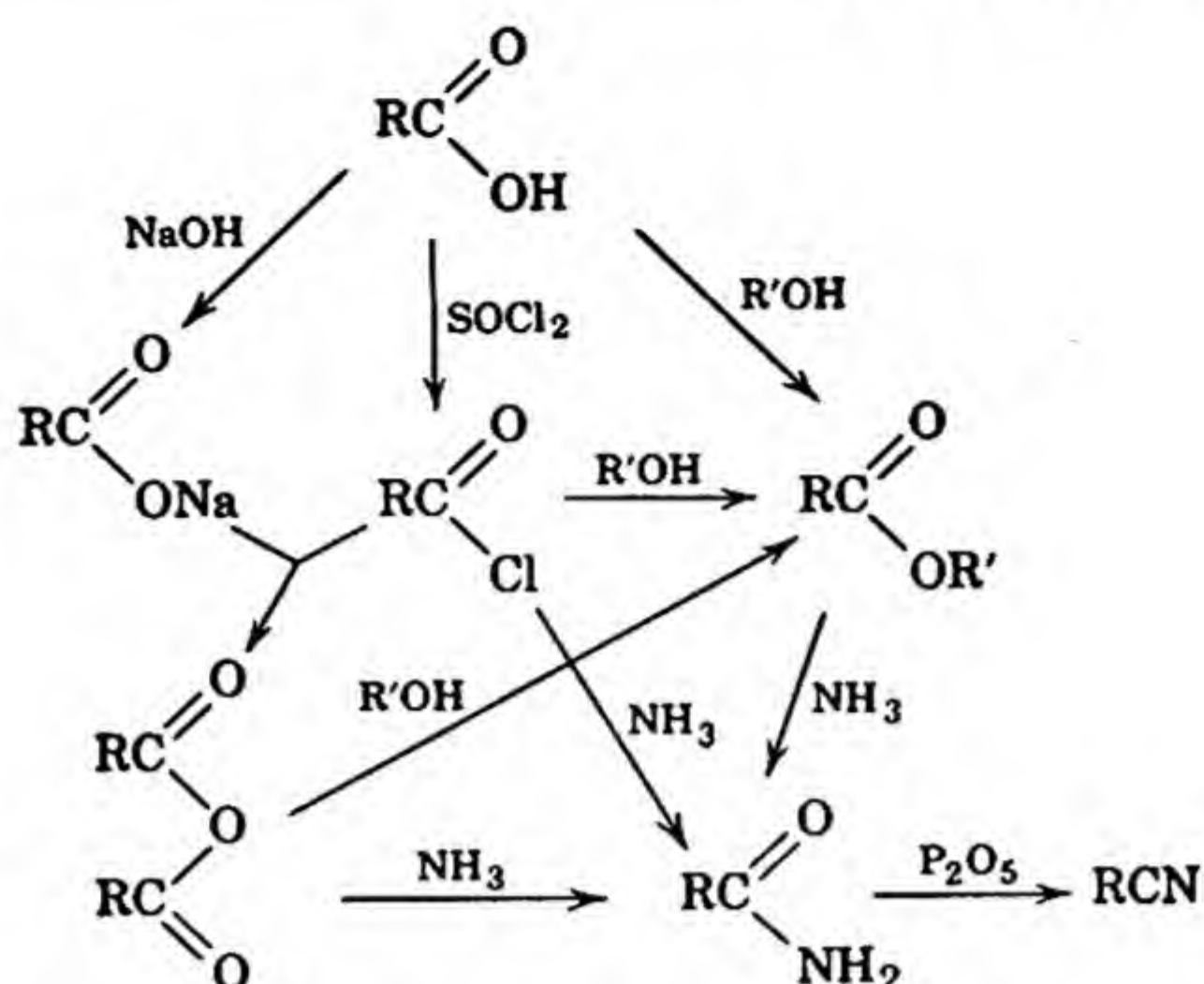
Like other acid derivatives, nitriles are hydrolyzed by aqueous alkali or, preferably, acid solutions. The amide is an intermediate and may sometimes be isolated.



Nitriles are named by reference to the parent acid.

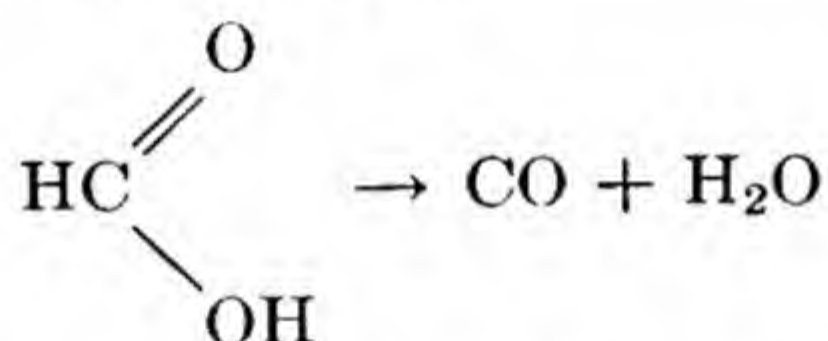


The relationship of the various acid derivatives can be seen in the following chart.

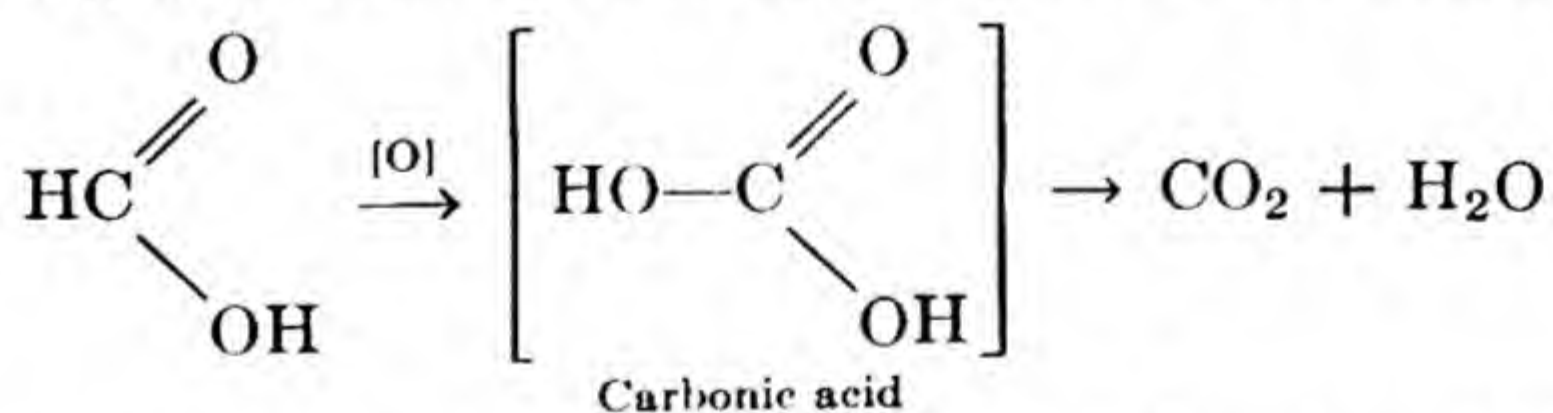


**Formic Acid and Its Derivatives.** Formic acid is a colorless liquid which boils at  $101^\circ$ . It is a poison and has a vesicant (blistering) action on the skin. This property is largely responsible for the painful effects of the stings of nettles and of some insects.

Formic acid has certain properties different from those of other acids. For example, it undergoes dehydration in the presence of sulfuric acid to yield carbon monoxide.

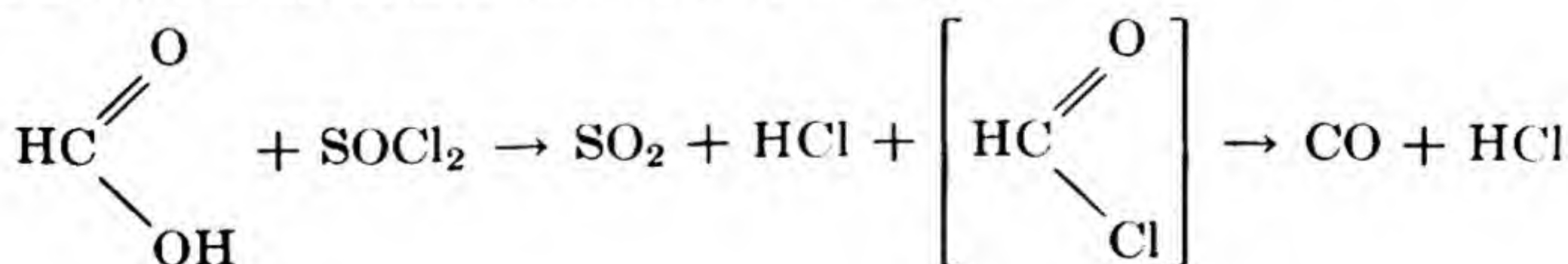


Furthermore, it is a reducing agent. Oxidizing agents such as potassium permanganate convert it to carbon dioxide and water. This be-



comes understandable when we consider that formic acid is also formally an aldehyde.

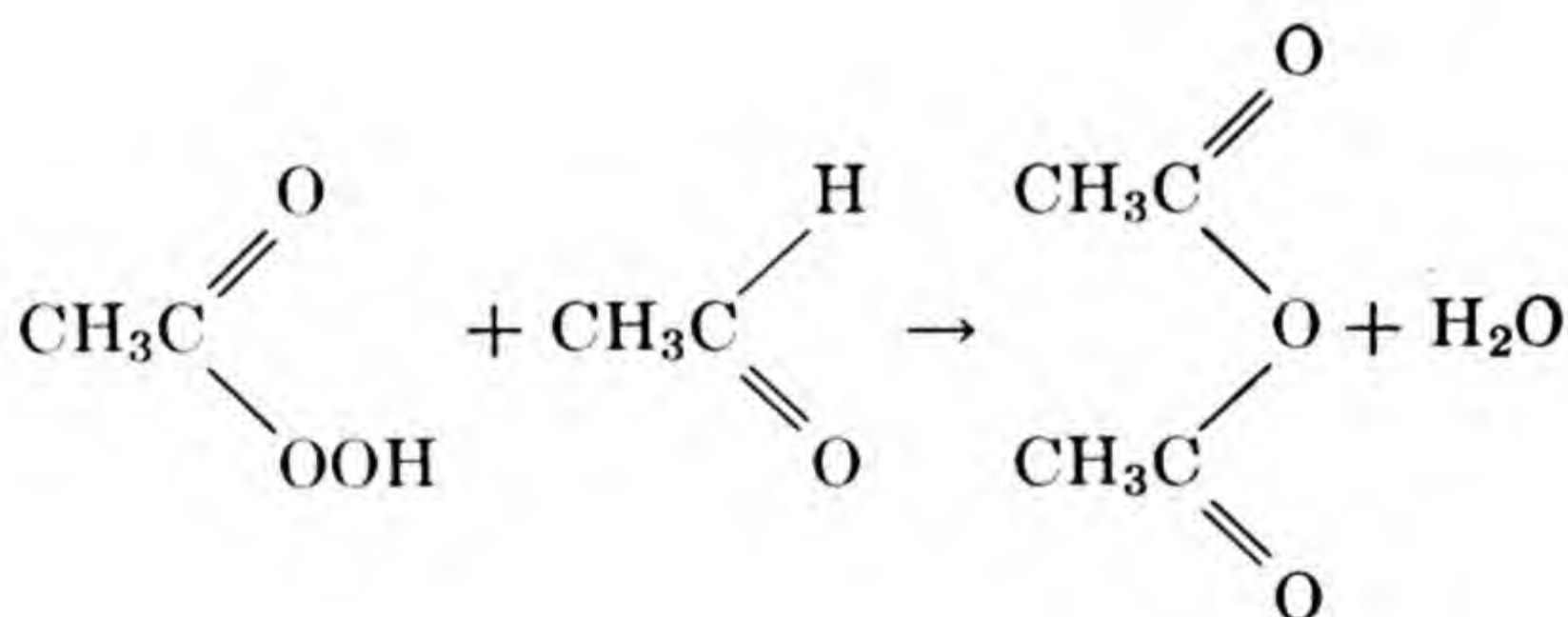
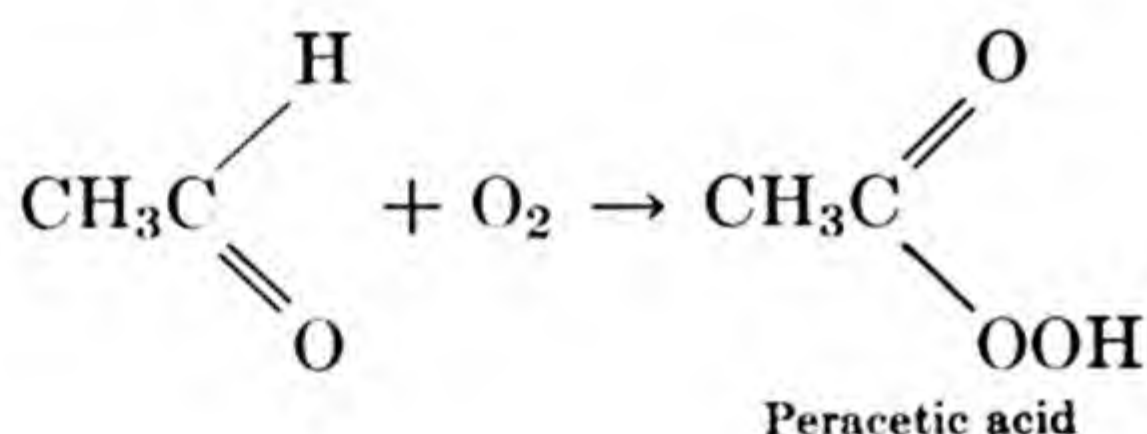
Formyl chloride and formic anhydride are not stable at ordinary temperatures. Attempts to make formyl chloride from formic acid yield carbon monoxide and hydrogen chloride.



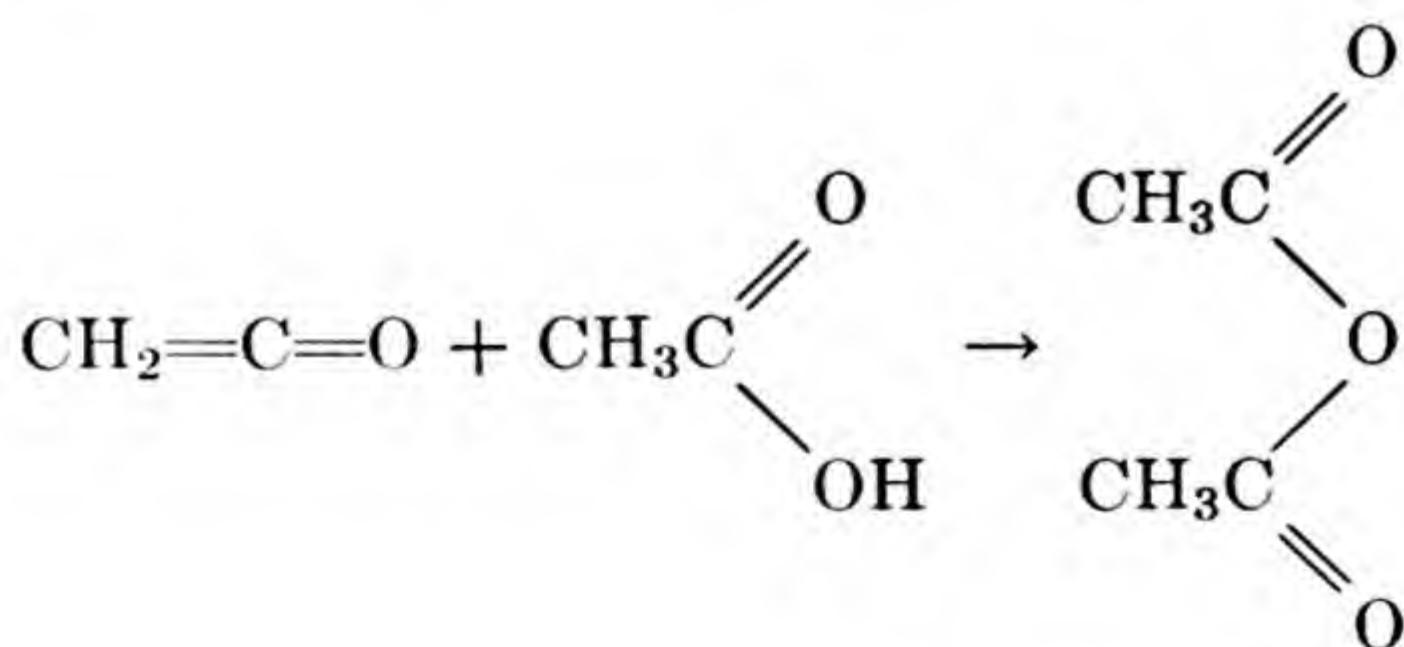


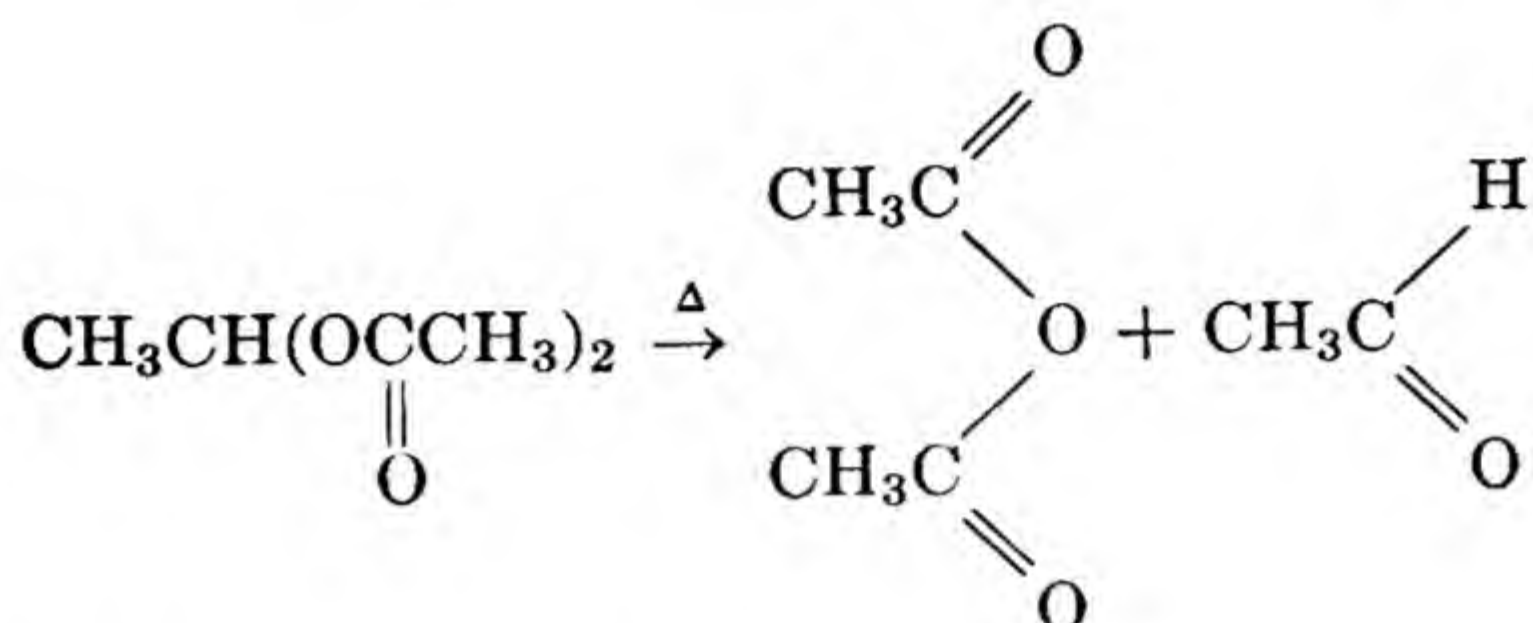
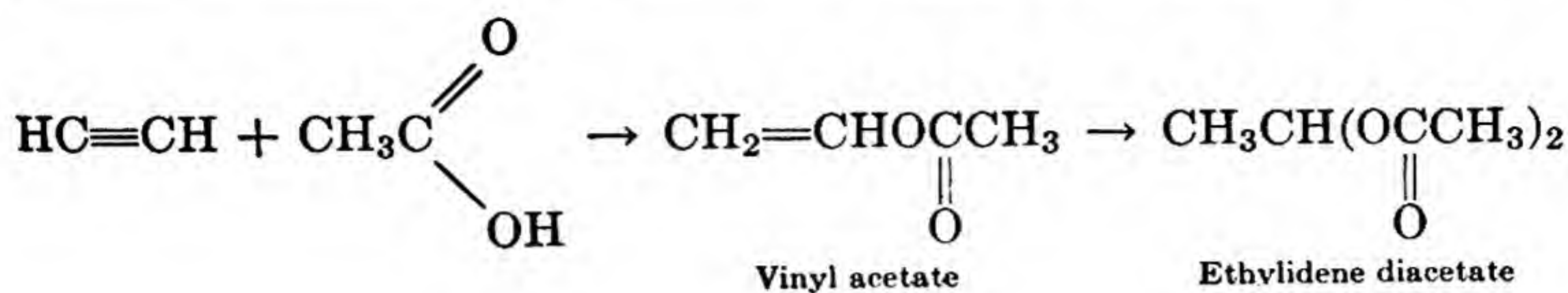
**Acetic Acid and Its Derivatives.** Acetic acid is a colorless liquid which boils at  $118^{\circ}$ . The pure acid crystallizes at  $16.5^{\circ}$  to an icelike solid, and for this reason is often known as glacial acetic acid. Like water, it is unusual in that freezing is accompanied by expansion. Most of the commercial product is obtained by the oxidation of acetaldehyde by air, but small amounts are produced in the distillation of wood. Vinegar, a dilute solution of acetic acid, is prepared by an oxidative fermentation of fruit juices.

A number of the derivatives of acetic acid, particularly ethyl acetate and acetic anhydride, are important commercial products. The esters of acetic acid, made by direct esterification, are used as solvents. Acetic anhydride, the bulk of which finds its way into cellulose acetate manufacture (Chapter 13), is made by several processes. The air oxidation of acetaldehyde under special conditions is one of these:

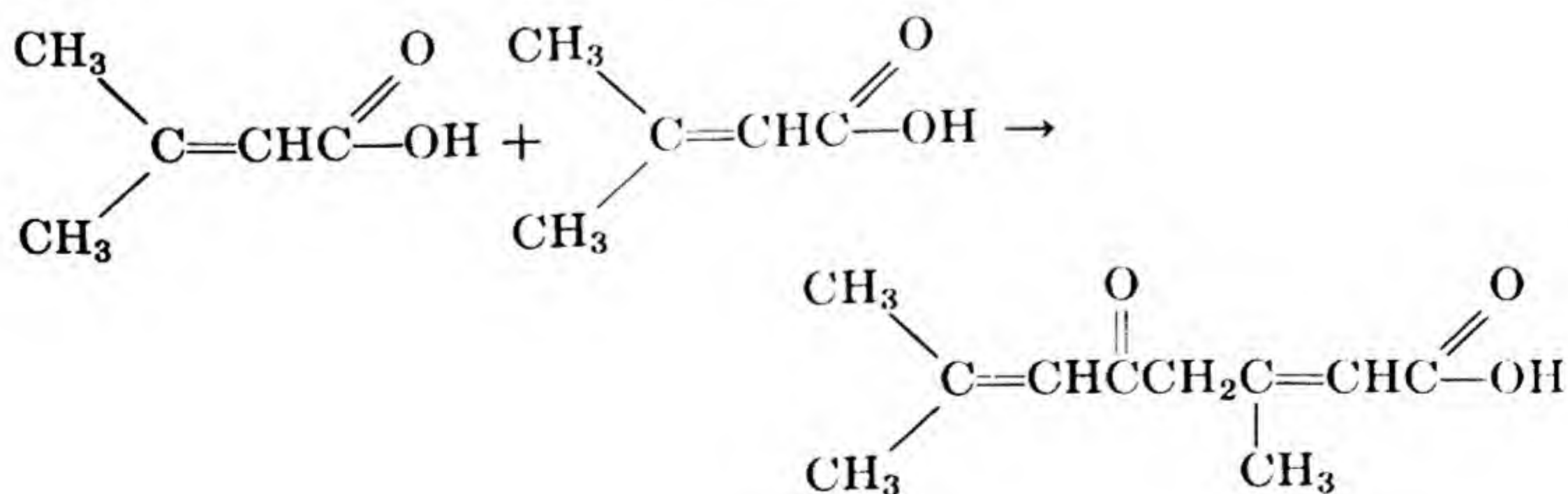
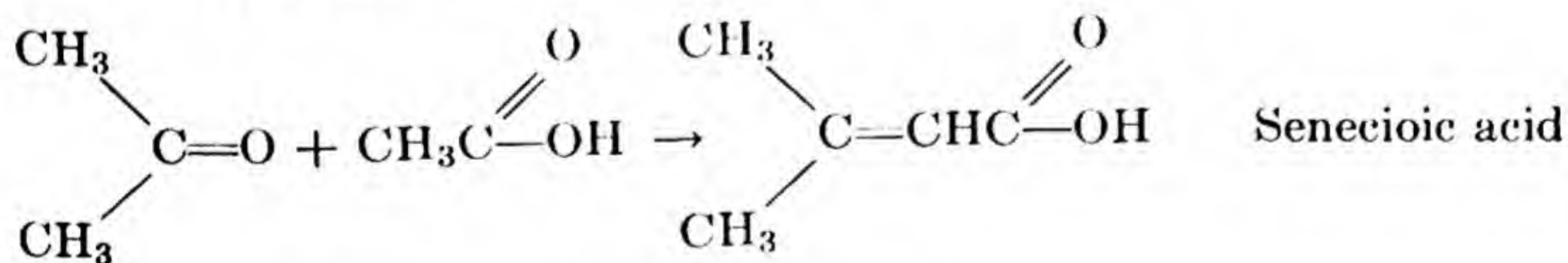
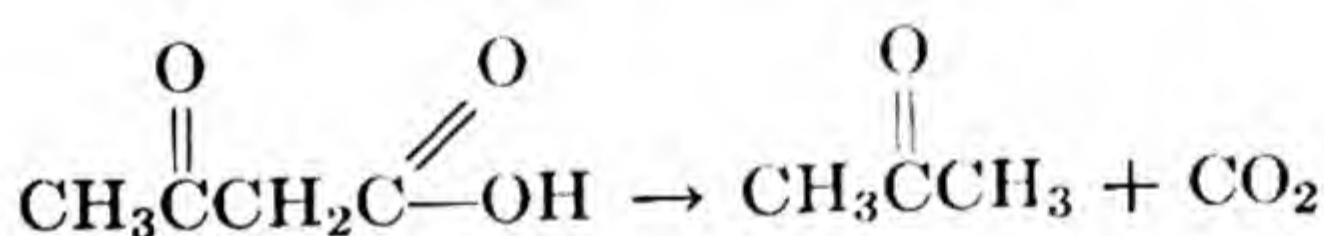
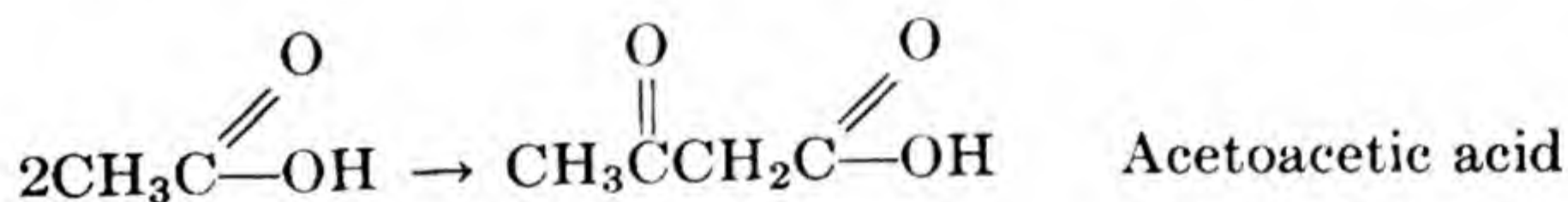


Acetic anhydride is also manufactured industrially from ketene and from acetylene.

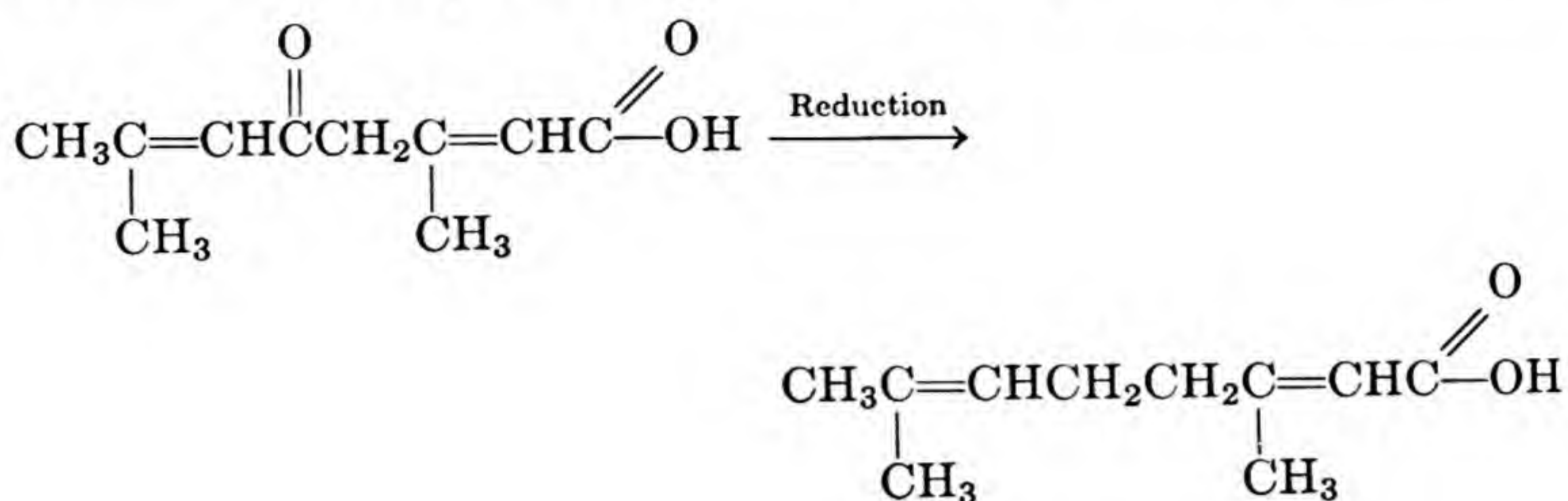




Acetic acid is an important substance from the biochemical standpoint. It is an intermediate in the oxidation of carbohydrates and fats by the body. Evidence has accumulated that the acetate ion is the raw material for the synthesis by plants of a variety of substances, such as terpenes and sterols. The polyisoprene chain in rubber, for example, may be built up according to the following scheme.







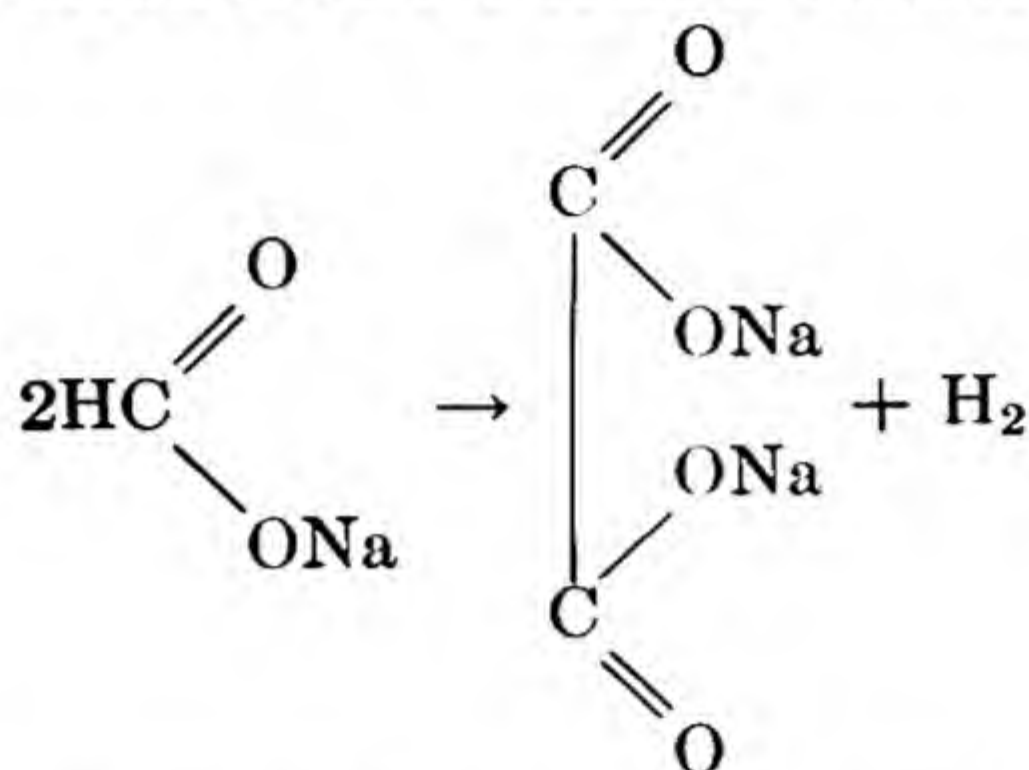
### ► DIBASIC ACIDS

Acids that have two carboxyl groups are said to be dibasic. The following table lists the first members of the series.

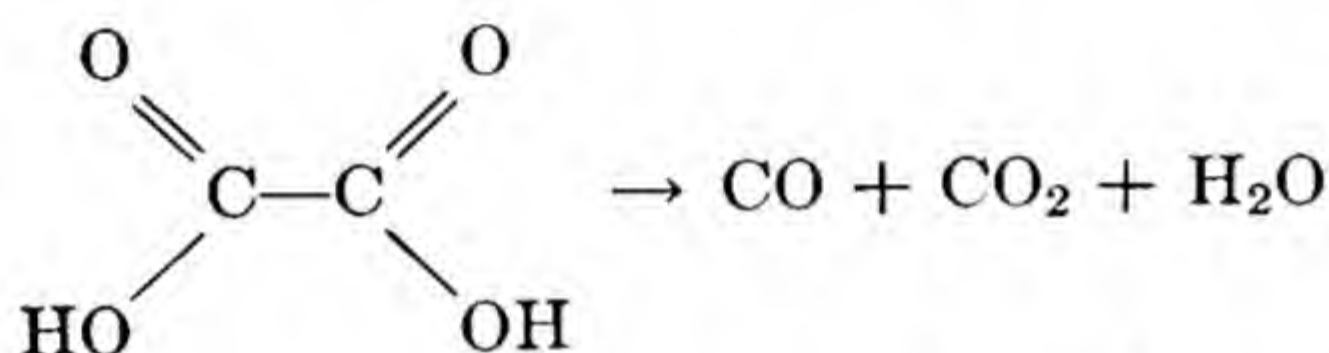
Name	Formula	Melting Point
Oxalic acid	$\begin{array}{c} \text{COOH} \\   \\ \text{COOH} \end{array}$	189°
Malonic Acid	$\begin{array}{c} \text{COOH} \\ / \\ \text{CH}_2 \\ \backslash \\ \text{COOH} \end{array}$	136
Succinic acid	$\begin{array}{c} \text{CH}_2\text{COOH} \\   \\ \text{CH}_2\text{COOH} \end{array}$	185
Glutaric acid	$\begin{array}{c} \text{CH}_2\text{COOH} \\ / \\ \text{CH}_2 \\ \backslash \\ \text{CH}_2\text{COOH} \end{array}$	98
Adipic acid	$\begin{array}{c} \text{CH}_2\text{CH}_2\text{COOH} \\   \\ \text{CH}_2\text{CH}_2\text{COOH} \end{array}$	157
Pimelic acid	$\begin{array}{c} \text{CH}_2\text{CH}_2\text{COOH} \\ / \\ \text{CH}_2 \\ \backslash \\ \text{CH}_2\text{CH}_2\text{COOH} \end{array}$	103

Oxalic acid, the simplest compound of the series, occurs in plants such as rhubarb, in urine, and in guano. It is used in calico printing, in dyeing, and as an ink remover. A wide variety of organic sub-

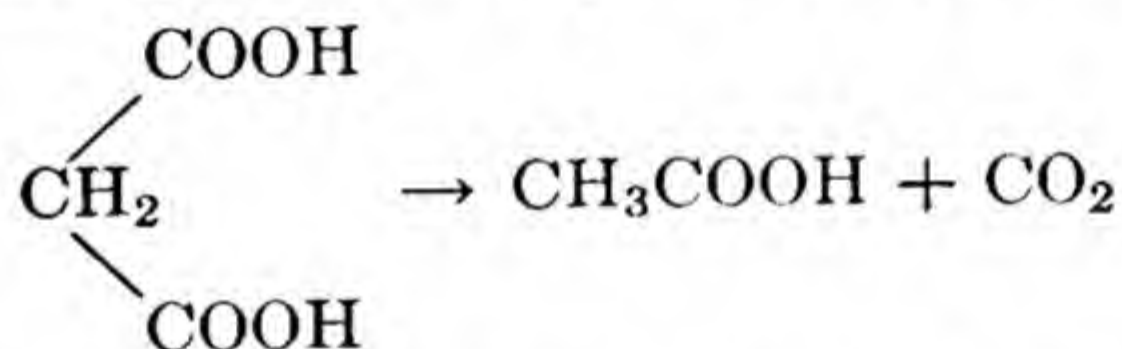
stances yield oxalic acid when subjected to vigorous oxidation. The commercial preparation involves heating sodium formate. The acid is obtained by acidification of the sodium oxalate produced.



The behavior of dibasic acids upon heating is of particular interest. Oxalic acid decomposes with the formation of carbon monoxide, carbon dioxide, and water, especially in the presence of dehydrating agents.

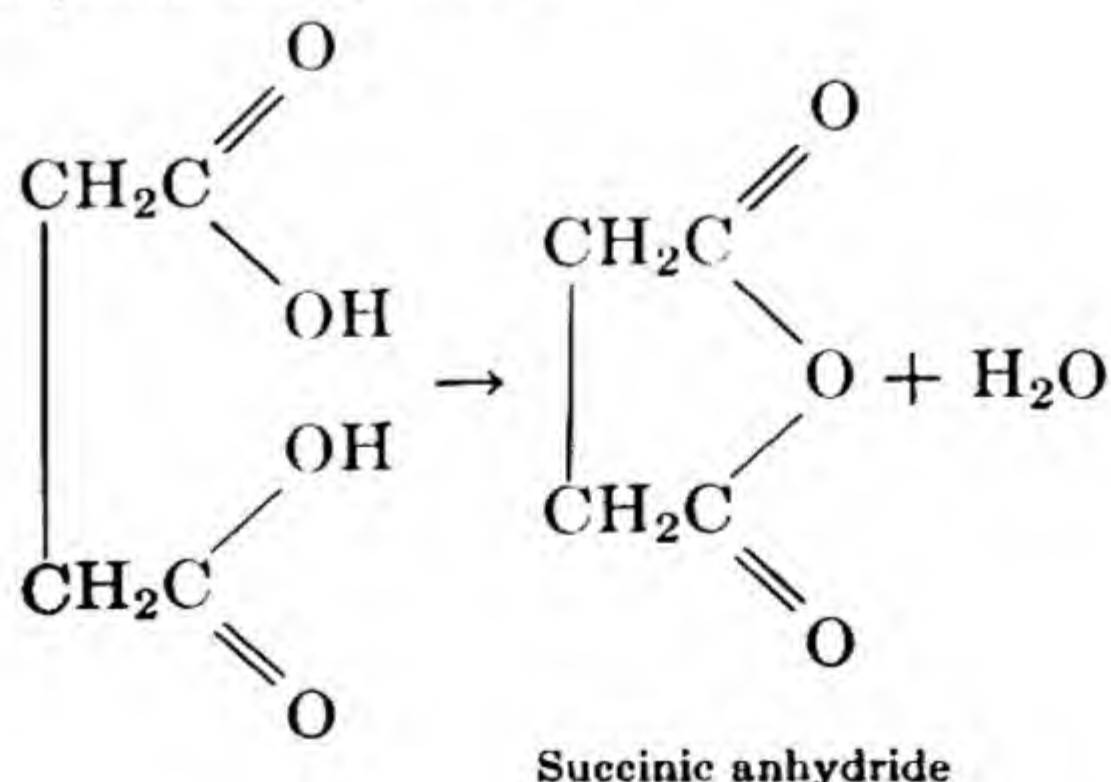


Malonic acid undergoes decarboxylation to yield acetic acid.



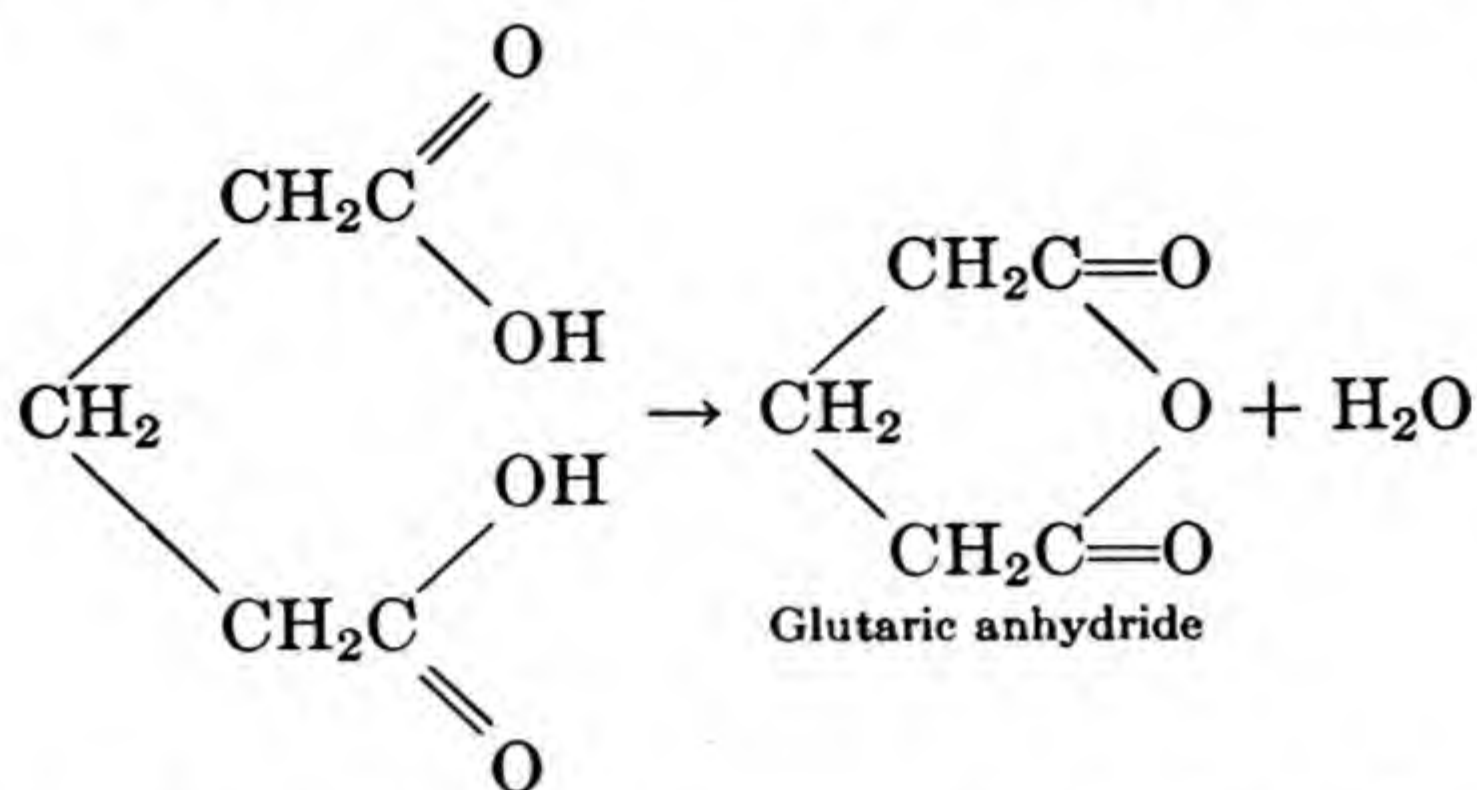
This behavior is general for acids having two carboxyl groups on the same carbon atom; that is, when heated, they lose one of the carboxyl groups as carbon dioxide, and a monobasic acid remains.

Succinic and glutaric acids readily lose water when heated to form the corresponding cyclic anhydrides.

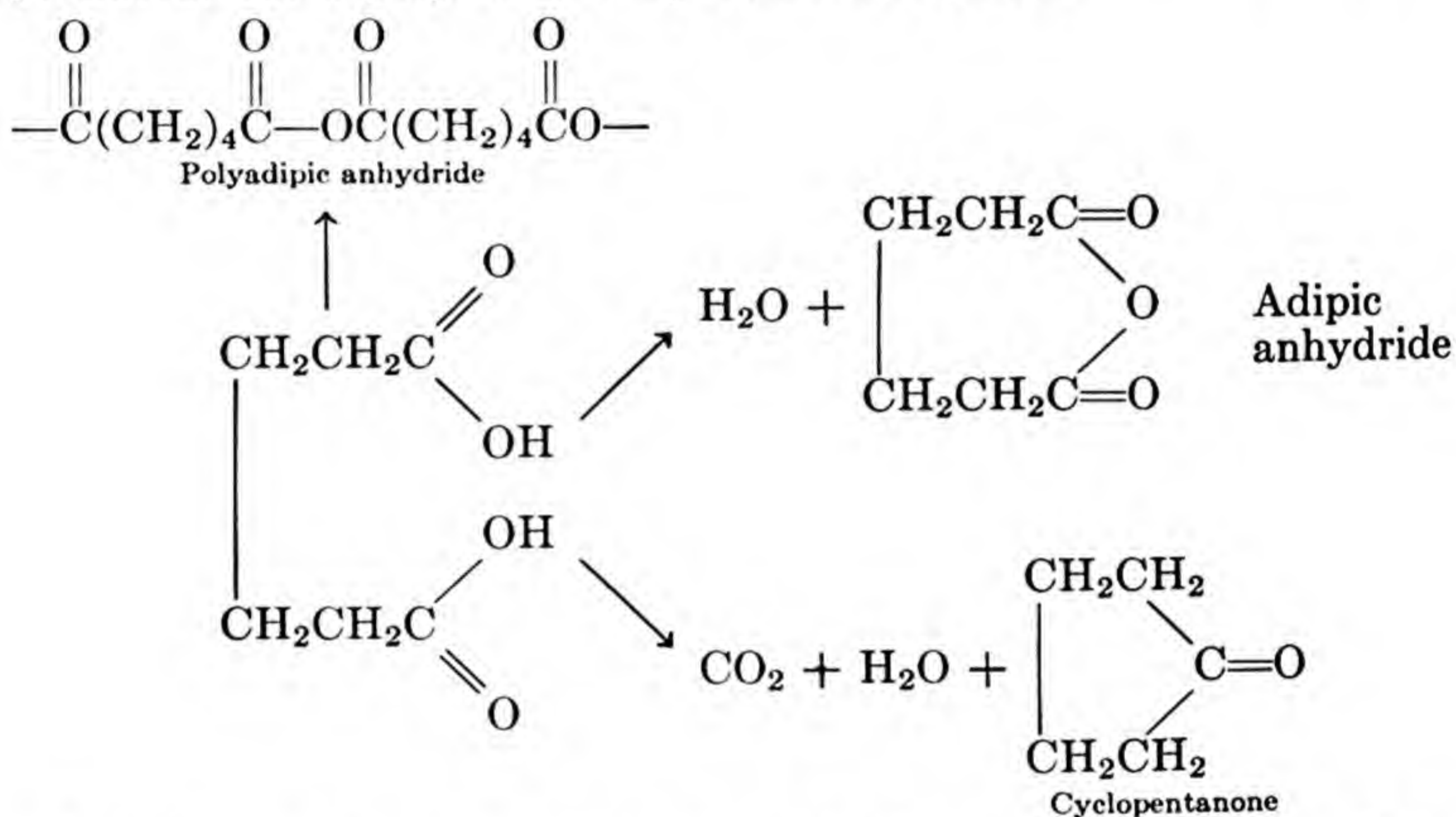


Succinic anhydride



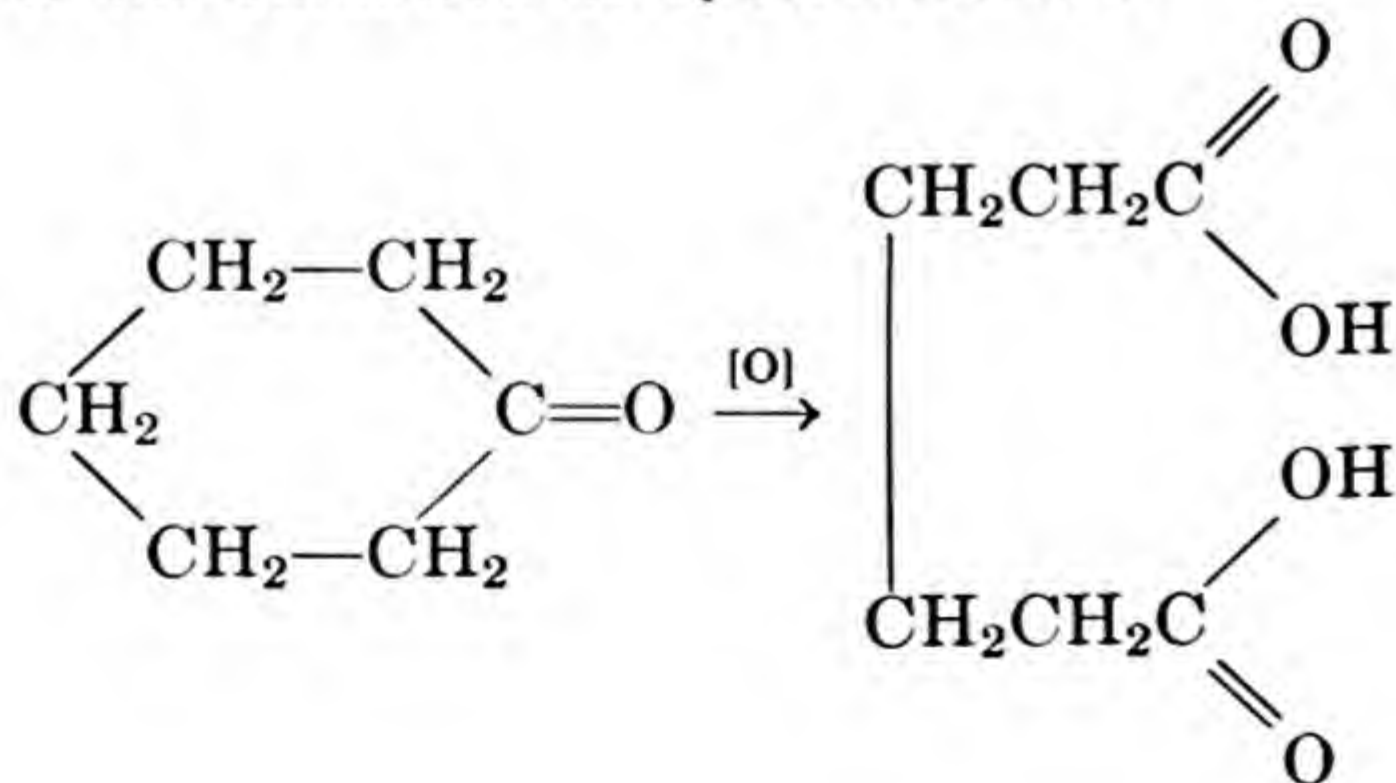


Adipic acid undergoes several concurrent reactions when it is heated. A small amount of cyclic anhydride is formed, and some ketone is produced, but a polymeric anhydride also results.

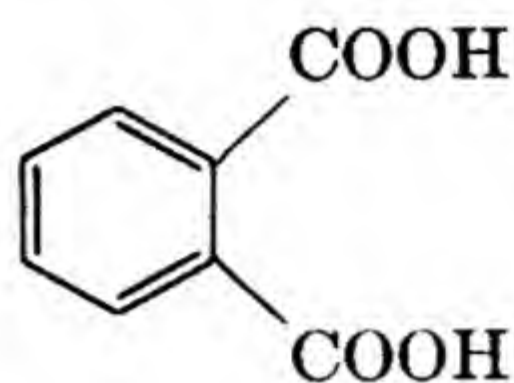


It is important to note the tendency in these reactions to form five- or six-membered rings whenever possible. This tendency is general and a consequence of the tetrahedral nature of the carbon atom.

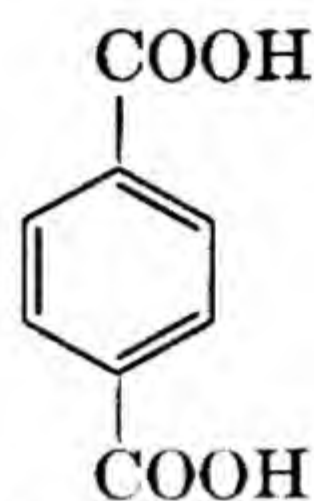
Adipic acid is made in tremendous quantities as an intermediate in nylon manufacture. Several processes are used to obtain the acid, one of which is the oxidation of cyclohexanone.



The most important aromatic dibasic acids are phthalic and terephthalic acids.

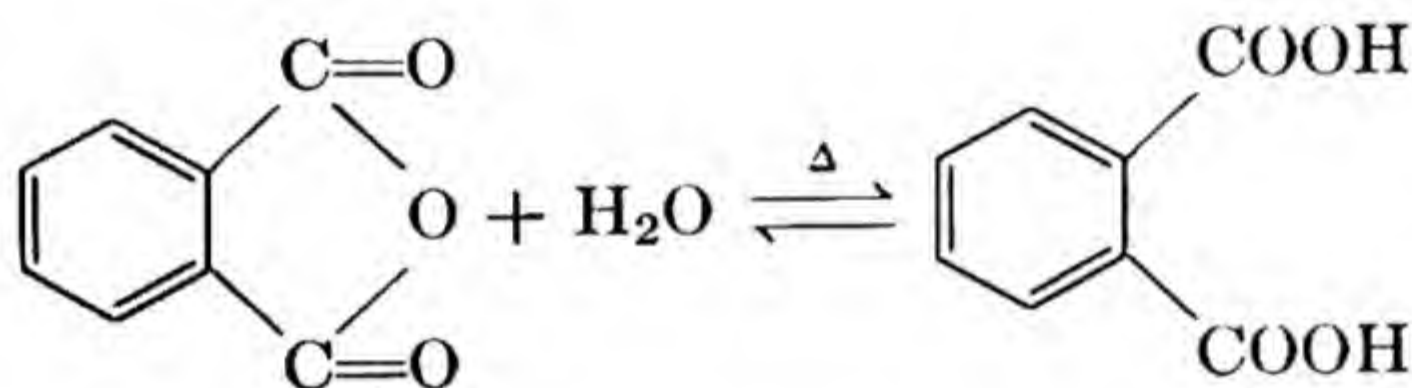
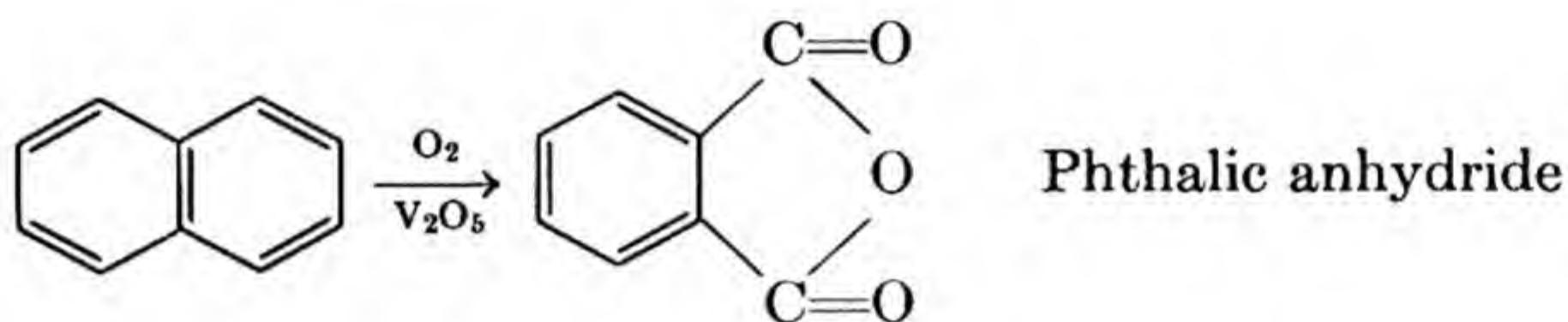


Phthalic acid

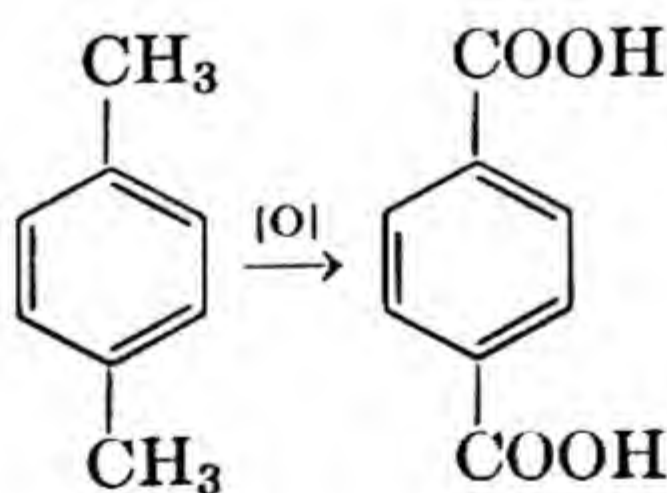


Terephthalic acid

Phthalic anhydride, readily hydrolyzed to the acid, is prepared by the air oxidation of naphthalene:

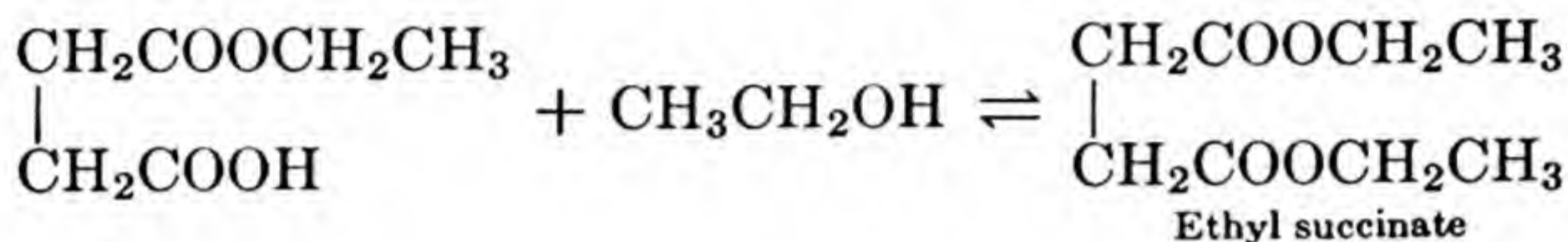
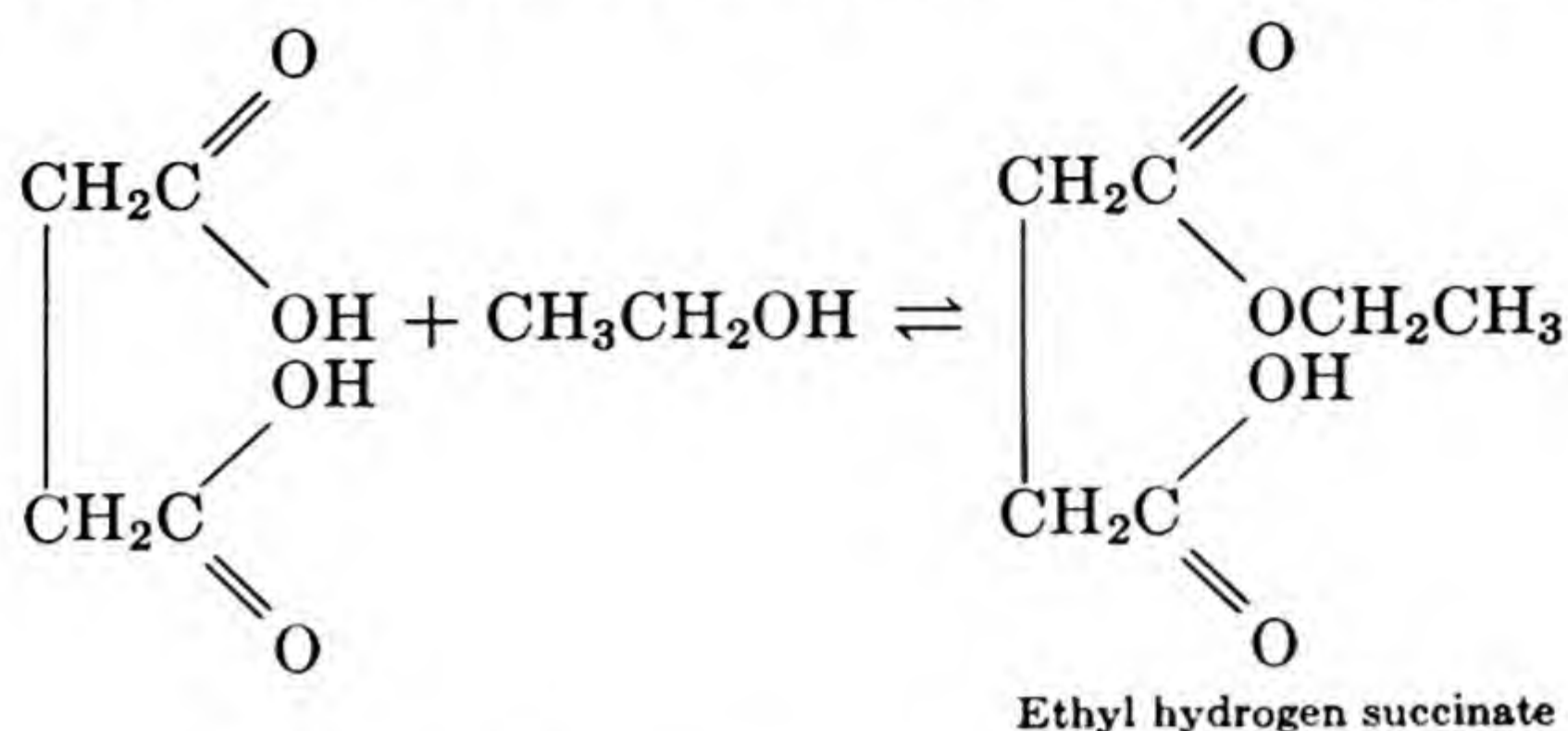


The anhydride serves in the manufacture of synthetic resins. Terephthalic acid, prepared by the oxidation of *p*-xylene, is employed in the manufacture of Dacron, a synthetic fiber.

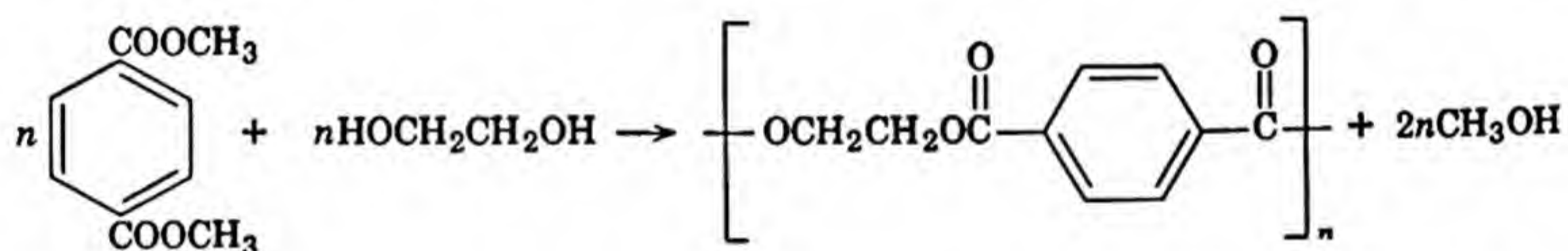


The dibasic acids in general form two series of acid derivatives. The esterification of succinic acid, for example, gives the mono- or diester.





Because of their difunctional character the dibasic acids have proved amenable to the preparation of polymers, some of which are valuable commercial products. Dacron is the trade name for polyethylene glycol terephthalate; it is made by the reaction of methyl



terephthalate with ethylene glycol. Like nylon, Dacron is available in fabrics of silklike or woollike appearance and texture. Dacron is used in large quantities blended with other fibers, such as wool or cotton.

Mylar is a film form of Dacron. It has great strength and fine electrical insulating properties. One of its interesting applications is in magnetic recording tape.

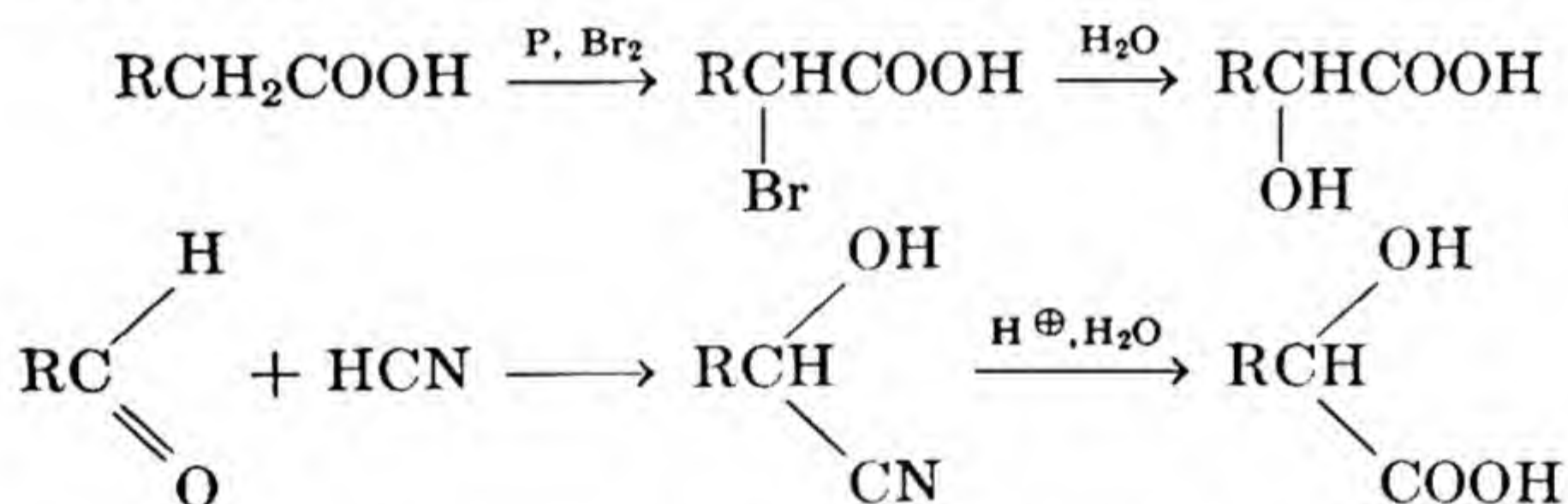
The alkyd resins obtained from dibasic acid anhydrides, such as phthalic anhydride, and polyalcohols, such as glycerol, are also important. They are employed for the most part in finishes. Nylon, also obtained primarily from dibasic acids, is considered in Chapter 14.

## ► HYDROXY ACIDS

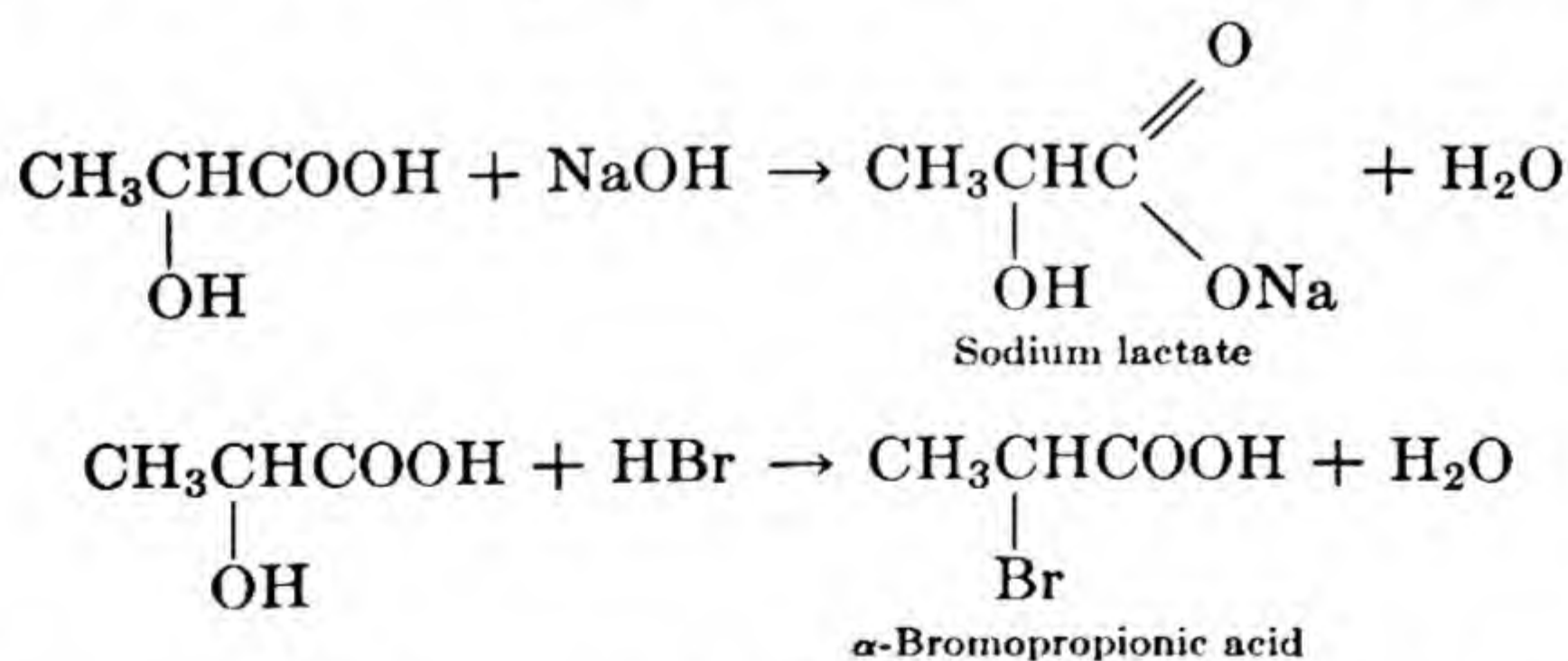
A number of hydroxy acids which occur naturally are given in the following table.

Formula	Name	Occurrence
$\text{HOCH}_2\text{COOH}$	Glycolic acid	Green apples, cane-sugar juice
$\text{CH}_3\text{CH}(\text{OH})\text{COOH}$	Lactic acid	Muscles, sauerkraut, sour milk
$\text{HOCH}(\text{COOH})\text{CH}_2\text{COOH}$	Malic acid	Fruits, maple sap
$\text{HOCH}(\text{COOH})\text{CH}(\text{COOH})\text{CH}_2\text{COOH}$	Tartaric acid	Fruits, wine fermentation (as a salt)
$\text{HOCH}(\text{COOH})\text{CH}_2\text{COOH}$	Citric acid	Citrus fruits; produced in various fermentations.

$\alpha$ -Hydroxy acids are often made synthetically from carboxylic acids or from aldehydes.



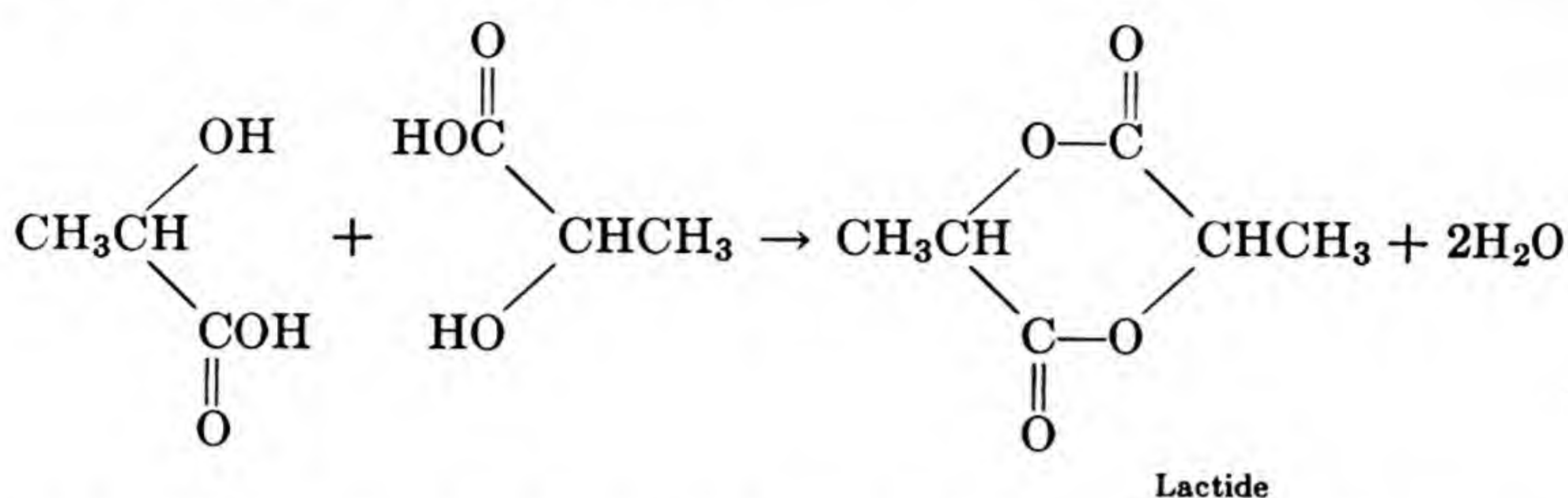
Since they possess the functional groups of both, hydroxy acids have properties of acids and alcohols. For example, they form salts readily and react with hydrohalogen acids to give halo acids:



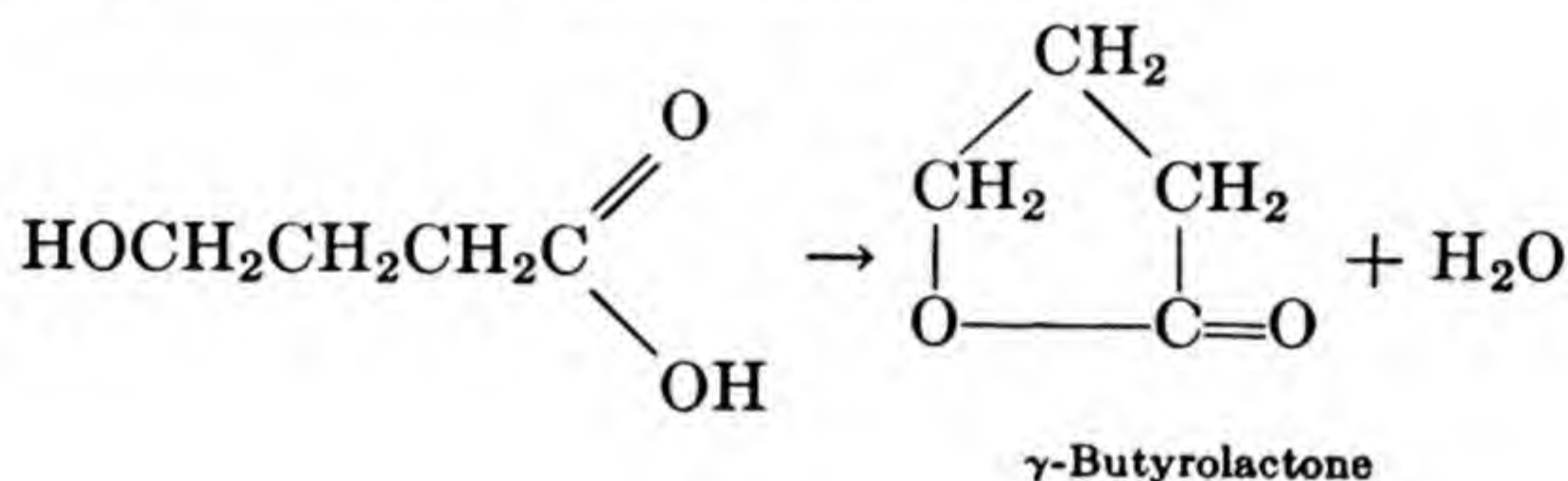
Certain of the hydroxy acids can react with themselves to form esters. Two molecules of lactic acid, for example, combine in the



presence of an acid to form lactide, a cyclic diester. This behavior is general for  $\alpha$ -hydroxy acids.

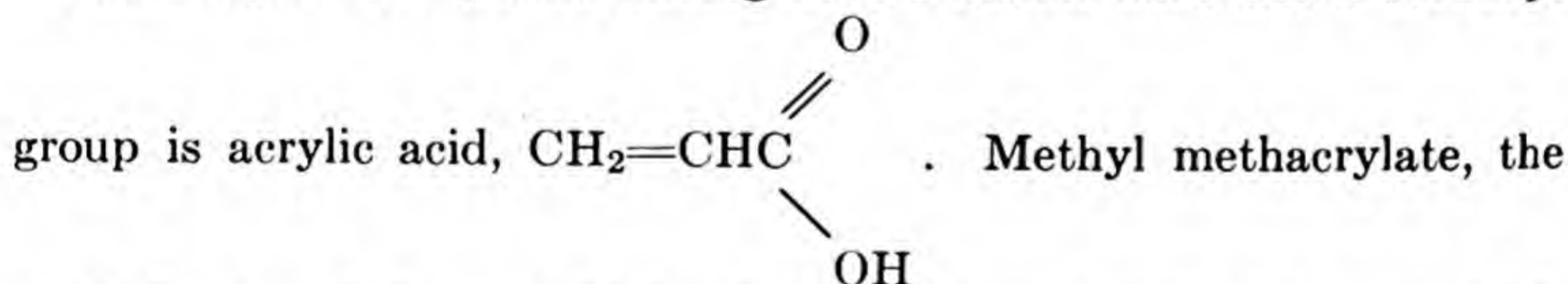


$\gamma$ -Hydroxy acids, on the other hand, react intramolecularly to produce lactones, which are cyclic monoesters.

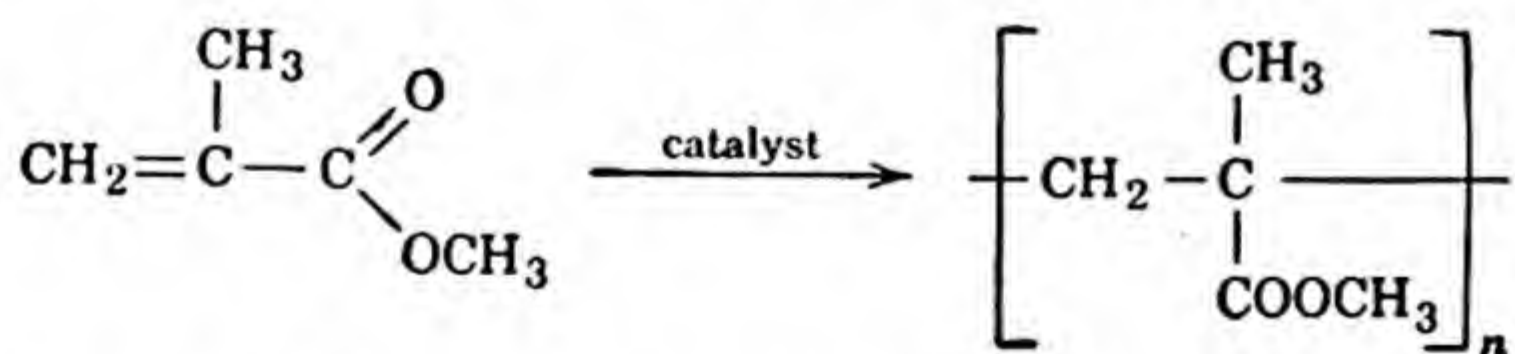


## ► UNSATURATED ACIDS

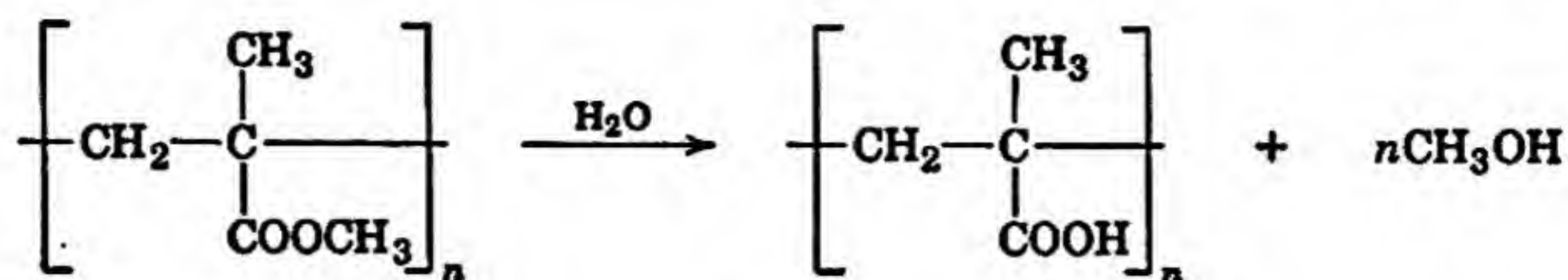
The simplest compound having both a double bond and a carboxyl



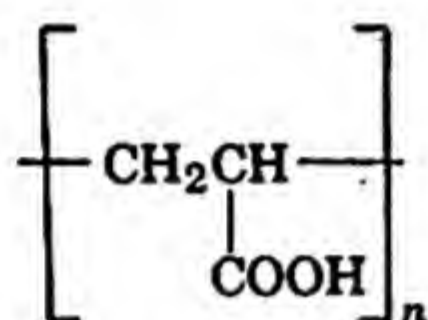
methyl ester of the next higher homolog, forms a solid polymer which is unusually transparent and so is used in airplane windows, gun turrets, and similar applications. It has advantages over glass in that it is lighter and less brittle, but it is more easily scratched. This plastic has been sold under the trade names "Lucite" and "Plexiglas."



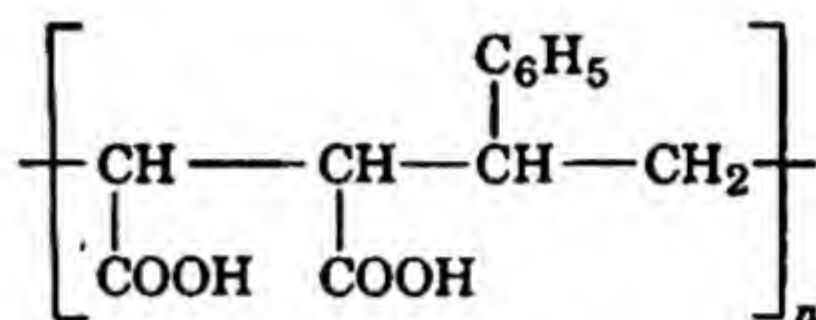
The hydrolysis of polymethyl methacrylate yields polymethacrylic acid, which has found application as a soil conditioner. Incorporated



into clay soils, soil conditioners improve their physical properties by forming aggregates which allow better penetration of water. Polyacrylic acid and the copolymer from styrene and maleic acid are also employed as soil conditioners. The cost of these agents has limited their employment to gardens and floriculture.

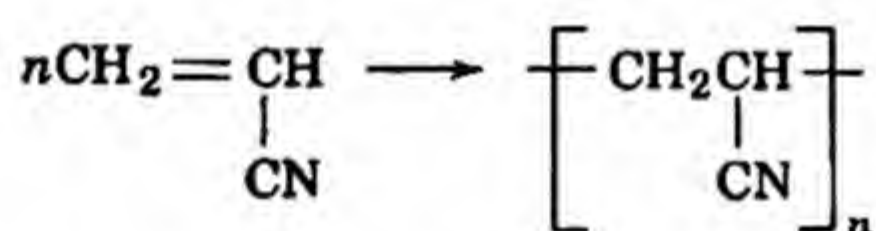


Polyacrylic acid



Styrene-maleic acid copolymer

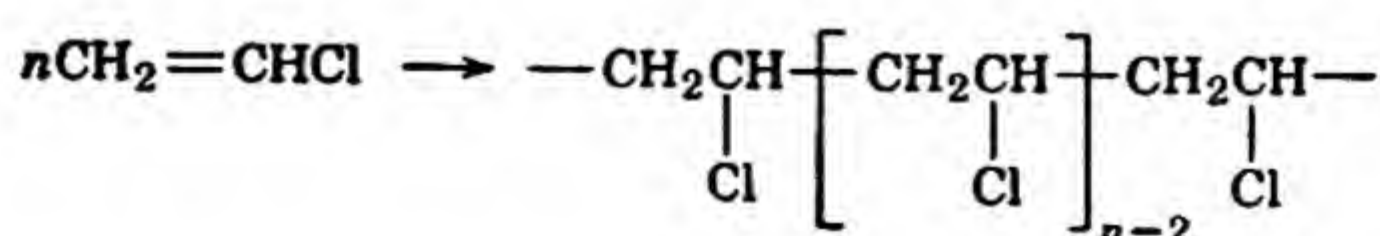
Various other polymers of commercial importance are obtained from acids or their derivatives. An example is polyacrylonitrile (Orlon), the primary application of which is in fabrics. Because of its strength and low water absorption it can be woven into fabrics which have good appearance and feel and are very resistant to out-



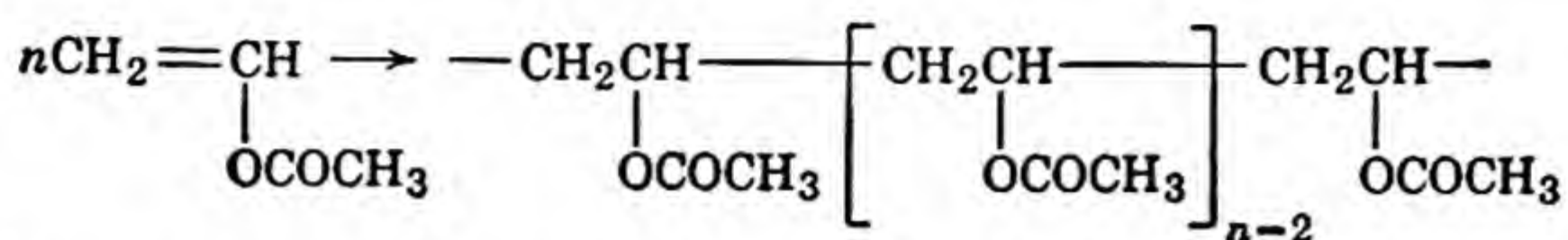
Polyacrylonitrile

door exposure. Perhaps the most difficult problem that had to be solved before polyacrylonitrile fibers could be widely used is their resistance to dyeing. Dyeability can be improved by copolymerizing acrylonitrile with other monomers (dynel, Acrilan). Polyacrylonitrile is often blended with other fibers such as wool.

Copolymers of vinyl chloride with vinyl acetate have proved to be plastics of very wide application. Vinyl chloride polymerizes by addition to yield polyvinyl chloride, which is high-melting, hard, and brittle. Polyvinyl acetate, on the other hand, is soft and sticky.

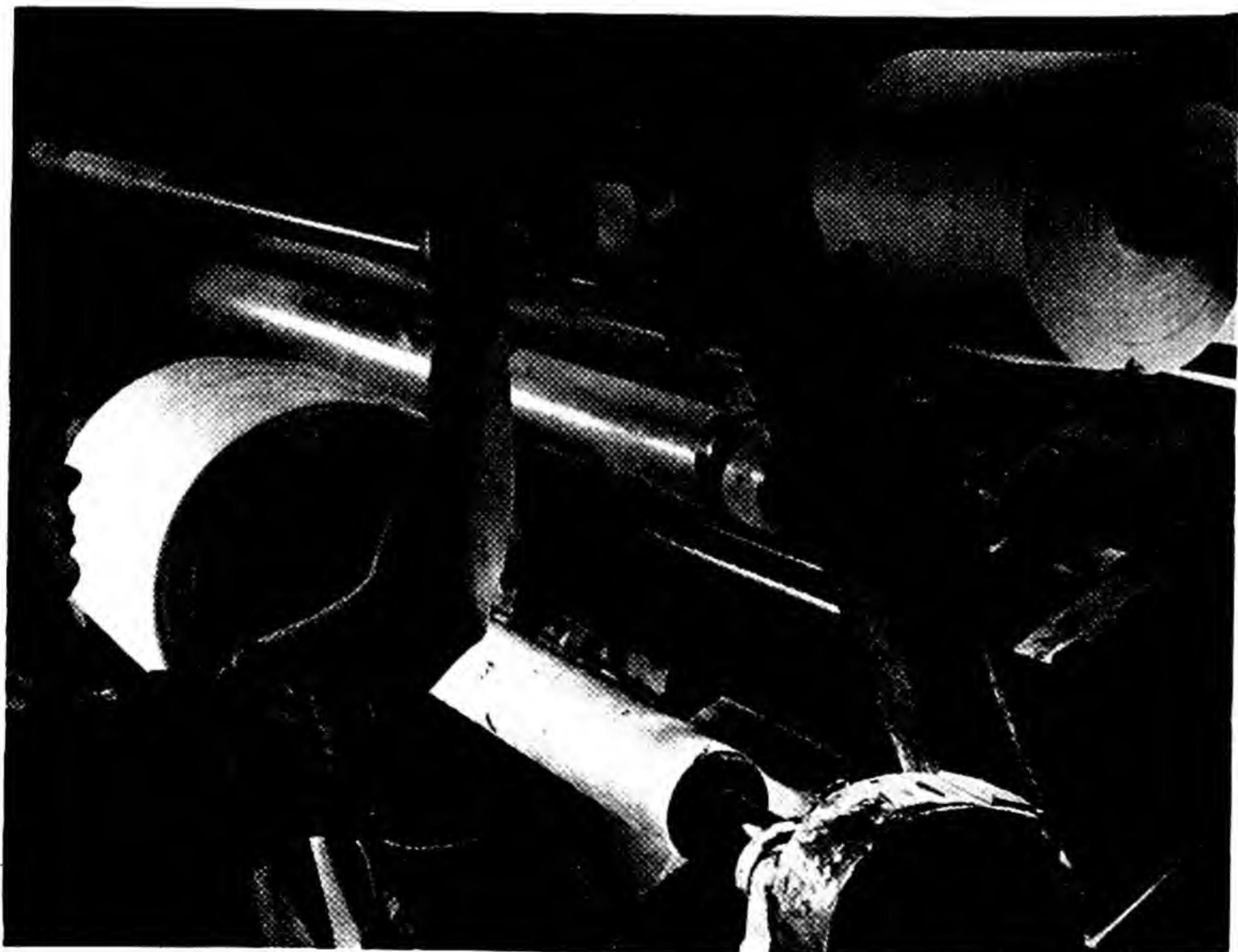






Both polymers have valuable applications. The copolymerization of vinyl chloride and vinyl acetate can be made to yield a variety of products with different properties by changing the ratio of the reactants. Additional variation is possible by the use of plasticizers such as esters of phthalic or adipic acid. Vinyl chloride-vinyl acetate copolymers have numerous applications. Pipe and tubing, screening, phonograph records, coated fabrics, and adhesives are examples.

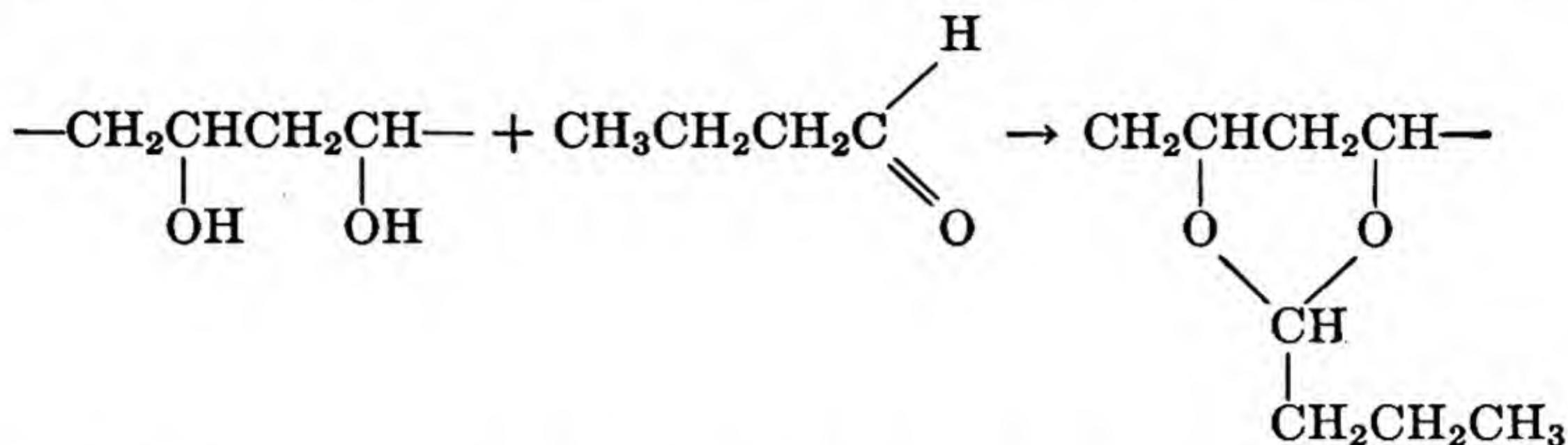
Large amounts of polyvinyl acetate are used in the manufacture of safety-glass interlayers. The acetate is partially hydrolyzed so that the polymer contains both hydroxyl and acetate groups. The new polymer is treated with *n*-butyraldehyde, which reacts with some of the hydroxyl groups to yield cyclic acetal groups. For the optimum



The final step in the manufacture of polyvinyl butyral for use in safety glass interlayers. The sheet is here being cut to the width required by the manufacturer of the safety glass. (Photograph courtesy of the Du Pont Company.)



properties the reactions must be carefully controlled. Safety glass

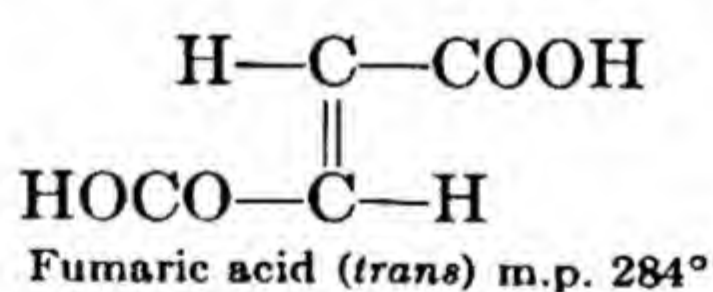
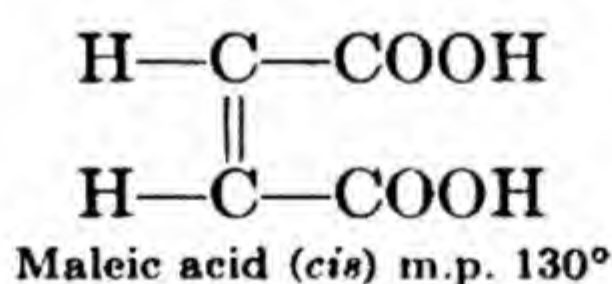


contains two sheets of glass with a layer of plastic between. In the event of breakage, shattering is not propagated through the interlayer.

As previously mentioned, polyvinyl acetate can be hydrolyzed to a polymeric alcohol. Numerous “polyvinyl alcohols” are made by using polyvinyl acetates of various molecular weights and by controlling the degree of hydrolysis. Some of these substances dissolve in water to give viscous solutions which can be used as adhesives or for “starching” clothes. Polyvinyl alcohol is also used in photographic film emulsions in place of gelatin.

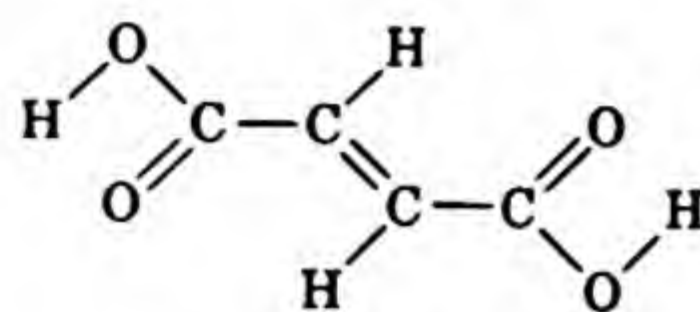
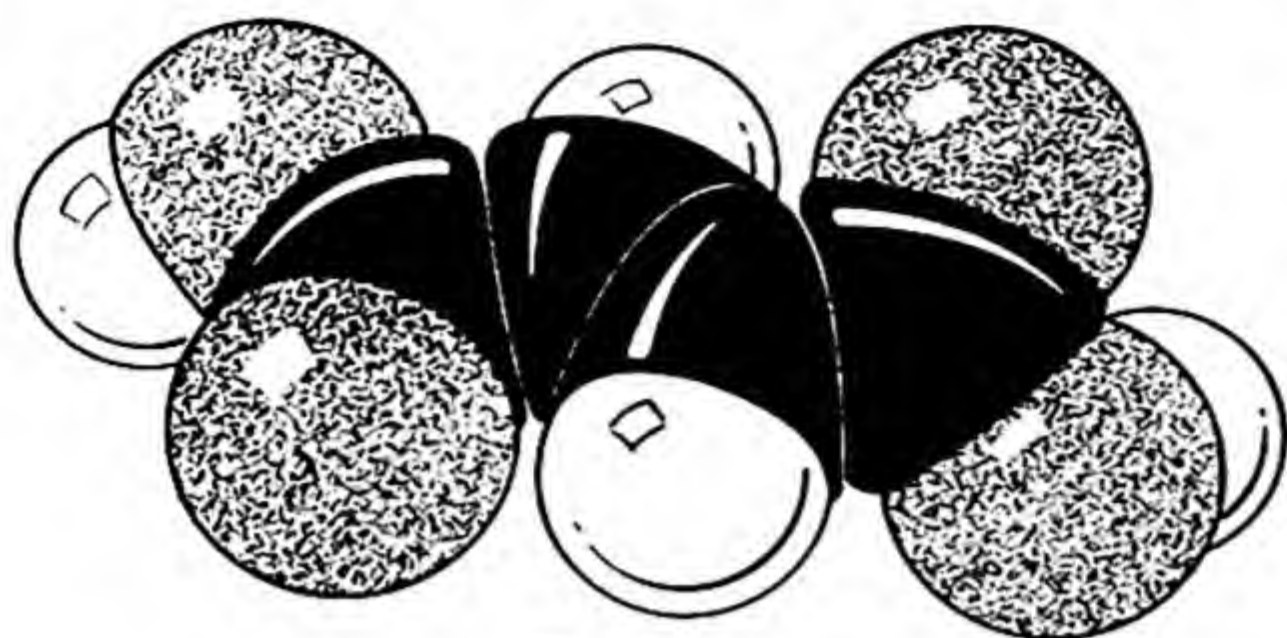
### ► CIS-TRANS ISOMERISM

Maleic and fumaric acids illustrate a type of isomerism not yet encountered. This type, called *cis-trans* or *geometric* isomerism, a variety of stereoisomerism, can arise when free rotation of one car-

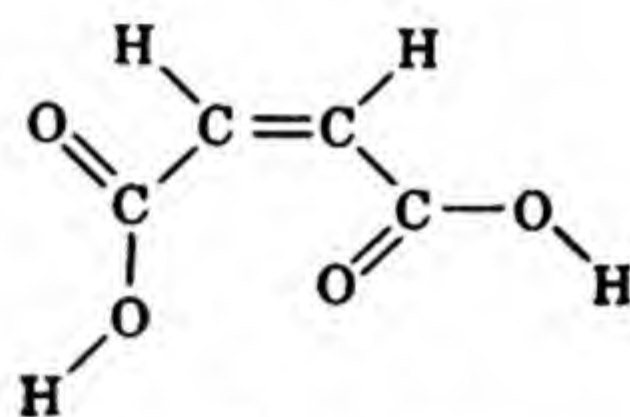
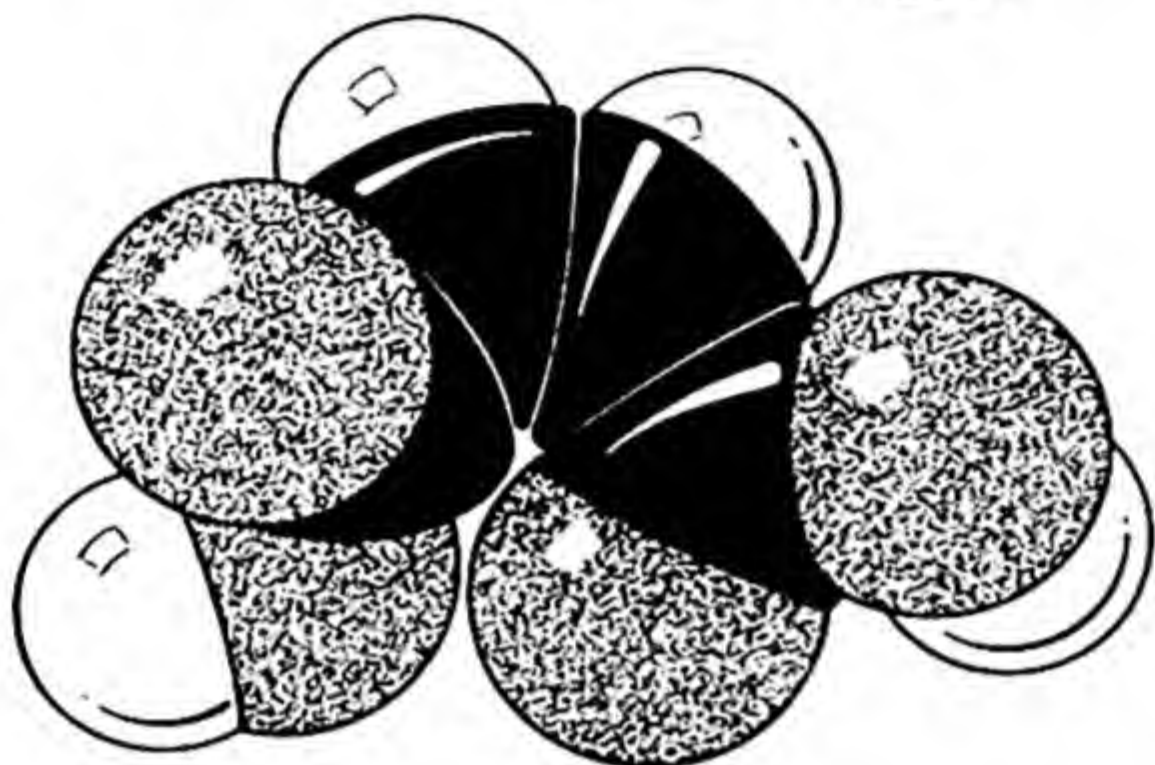


bon atom with respect to another is prevented. Though most single bonds allow free rotation, double bonds prevent it. Isomerism occurs when each of the two carbon atoms of the double bond has two unlike groups attached to it. When the two carbon atoms have identical substituents, the arrangement in which like groups occur on the same side of the double bond is said to be *cis*; the other is *trans*. Although in some cases the configuration is difficult to determine, with maleic and fumaric acids it is easy. The former produces a cyclic anhydride when heated, and because of the restriction of rotation by the double bond only the *cis* compound should do so. Maleic





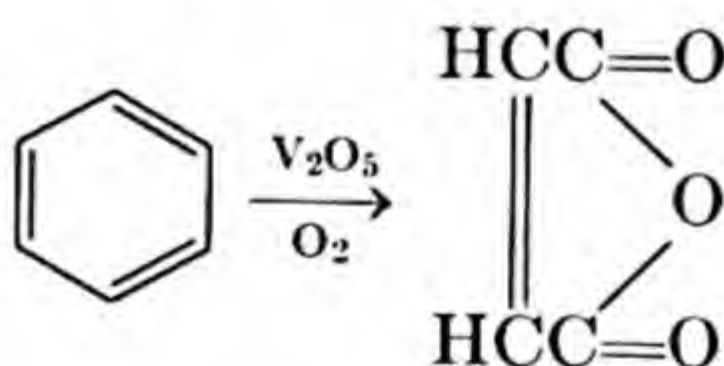
### Fumaric acid



### Maleic acid

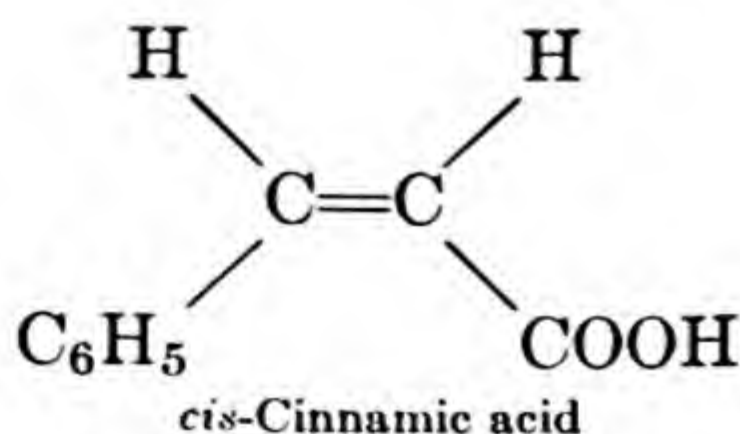
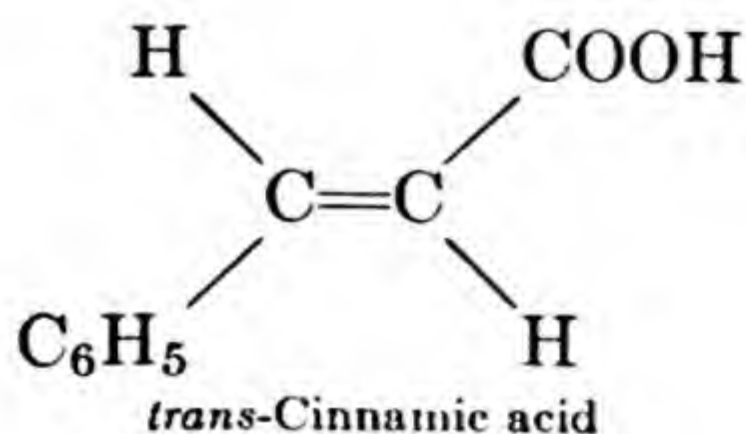
The *cis-trans* relationship of the maleic and fumaric acids, as well as the ready formation of maleic anhydride from maleic acid, is well shown in the models. On the other hand, the considerable distance between the carboxyl groups of fumaric acid would lead one to predict great difficulty in anhydride formation.

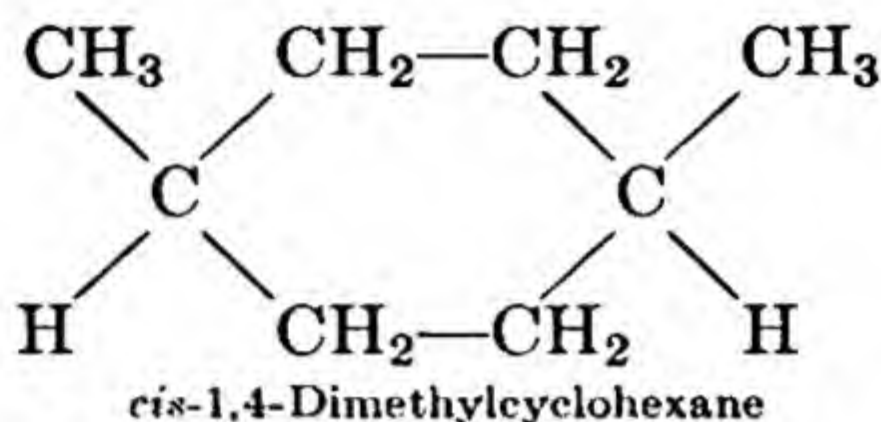
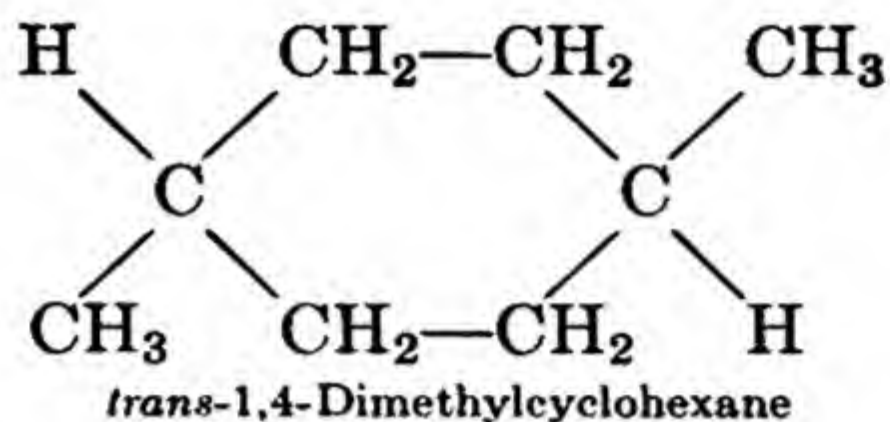
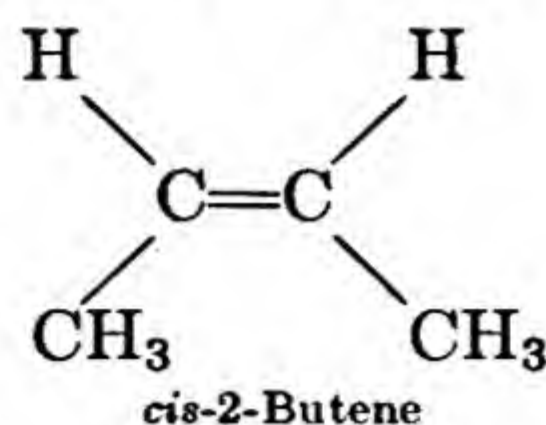
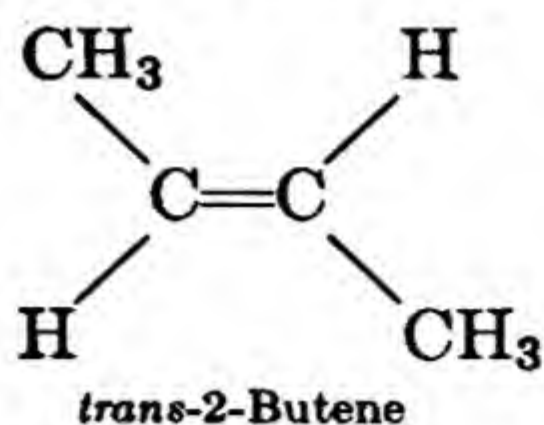
anhydride is used in the manufacture of certain synthetic resins and is obtained commercially by the catalytic oxidation of benzene.



Fumaric acid is found in muscle tissue and is an intermediate in carbohydrate metabolism in the body.

*Cis-trans* isomerism is of very common occurrence. Examples are given below.

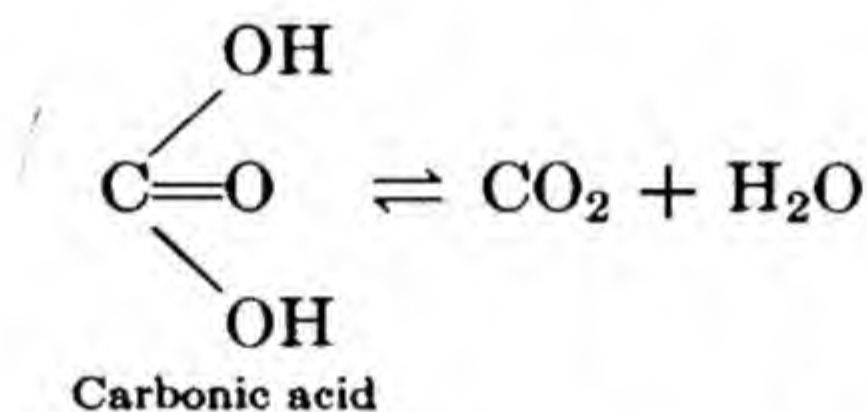




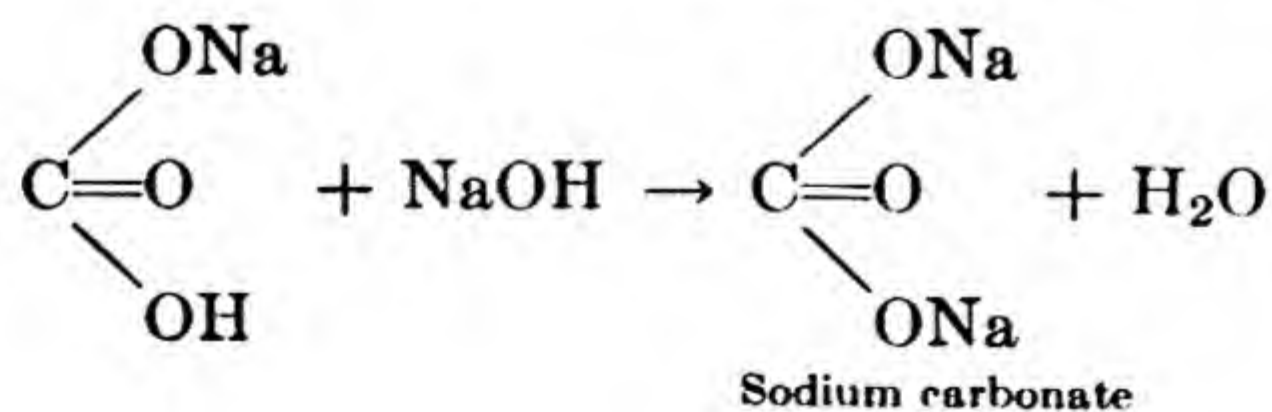
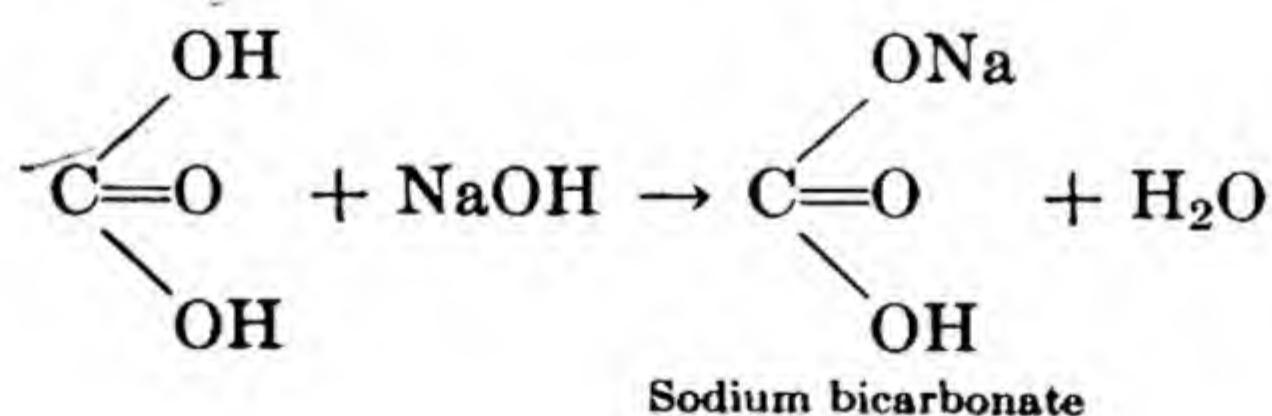
In the dimethylcyclohexanes the ring serves to restrict rotation. It is interesting that *trans* compounds are often more stable and higher melting than the *cis* compounds.

## ► CARBONIC ACID AND ITS DERIVATIVES

Carbonic acid has two hydroxyl groups attached to the same carbon atom and, like most such compounds, it is unstable; it is known only in dilute solution.

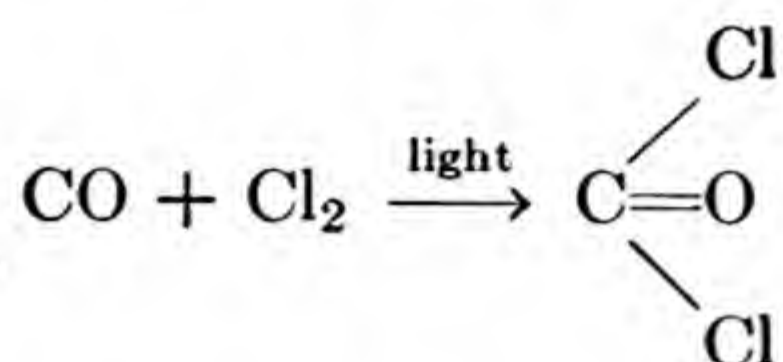


Carbonic acid, however, forms two series of stable salts. Depending upon the ratio of the two reactants, carbon dioxide or carbonic acid reacts with sodium hydroxide to give either sodium bicarbonate or sodium carbonate.

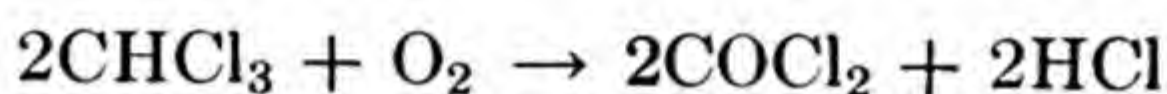




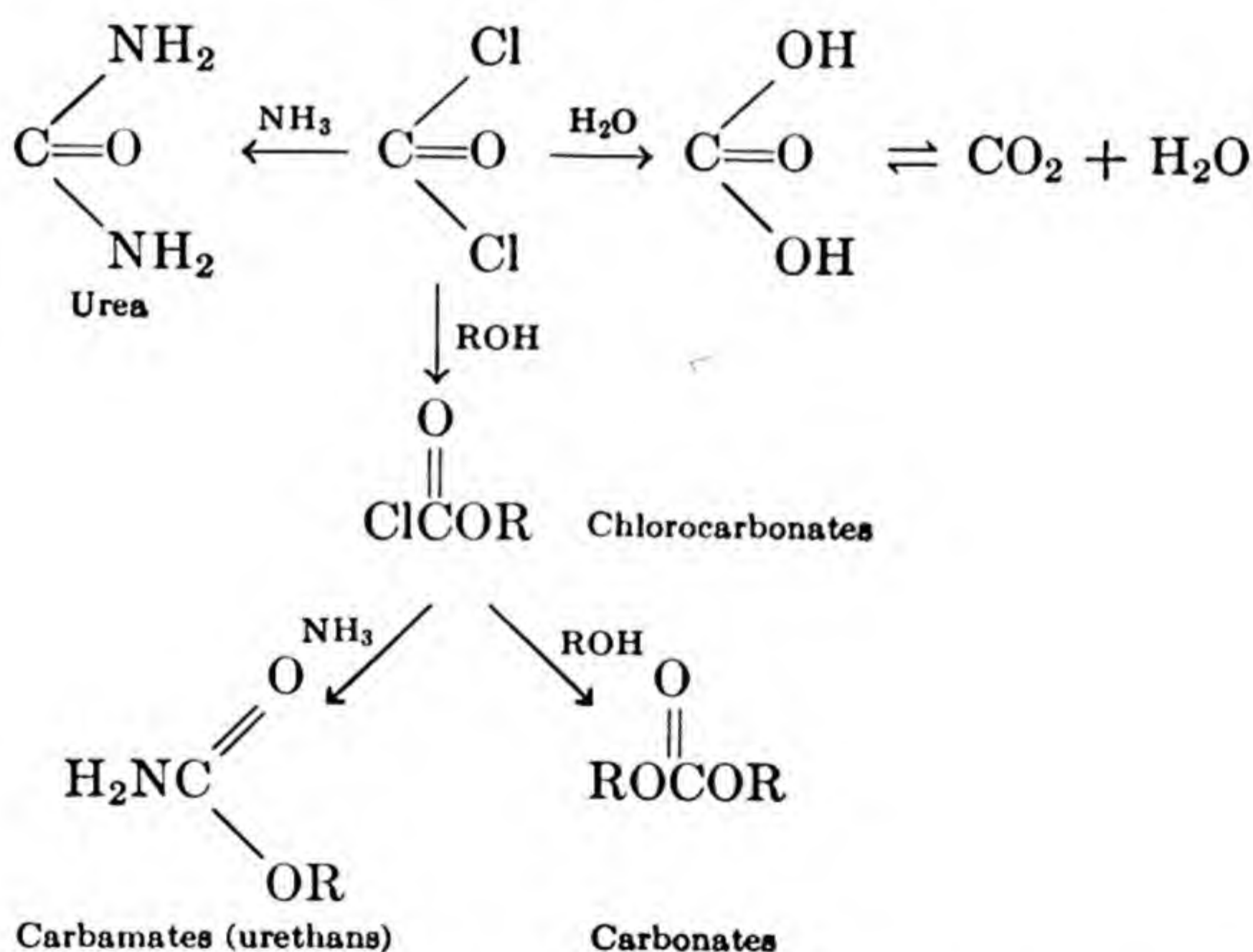
Many other derivatives of carbonic acid are known. Most are available from phosgene, the acid chloride, which is prepared by the combination of carbon monoxide with chlorine.



Phosgene is a very poisonous substance and, on this account, was used as a chemical warfare agent in World War I. It is also produced by the slow autoxidation of chloroform.

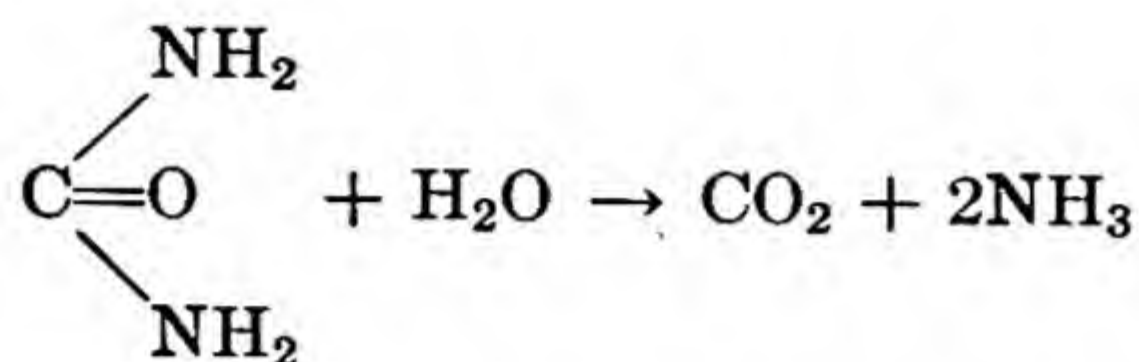


The following chart shows a few of the reactions of phosgene, which are essentially those of an acid chloride:

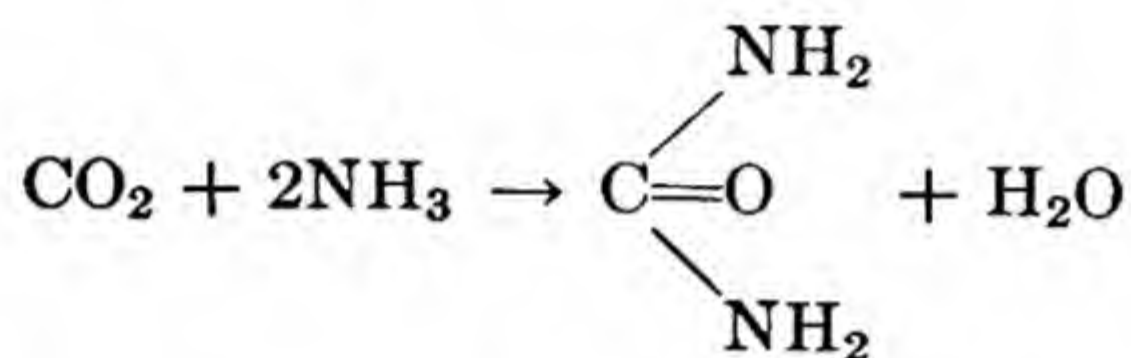


Urea is perhaps the most important of the derivatives of carbonic acid. It is the final product in the metabolism of proteins in man. An adult normally excretes 20–30 grams of urea in the urine per day. This amount corresponds to 80% of the nitrogen excreted by this route. Urea is also of interest historically as the first organic compound to be synthesized from so-called inorganic substances. The synthesis was accomplished by Wöhler in 1828 from ammonium sulfate and potassium cyanate.

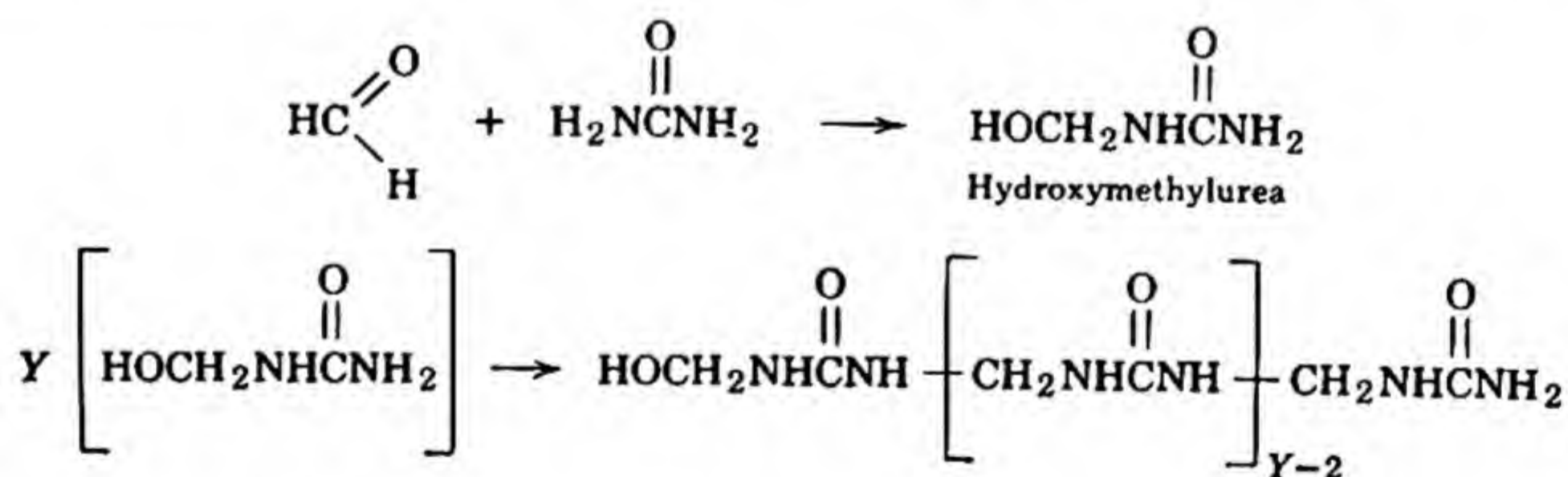
Urea may be regarded as the amide of carbonic acid and, indeed, is occasionally called carbamide. Hydrolysis converts it to carbon dioxide and ammonia.



In the commercial method of preparing urea the foregoing reaction is reversed: carbon dioxide and ammonia are heated together under pressure.

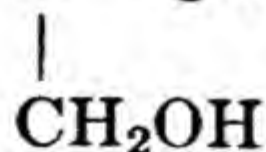


Urea is used in fertilizers, as a source of nitrogen in cattle feeds, and as a component of certain tooth powders. It serves in the preparation of barbiturates and a number of "plastic" materials. When urea and formaldehyde are heated together a solid polymeric substance is formed. A plausible explanation of the reaction is that urea reacts with the aldehyde to give hydroxymethylurea, which condenses with itself by the elimination of water to form a polymer.



At this stage the polymer (said to be linear) is of a sirupy consistency.

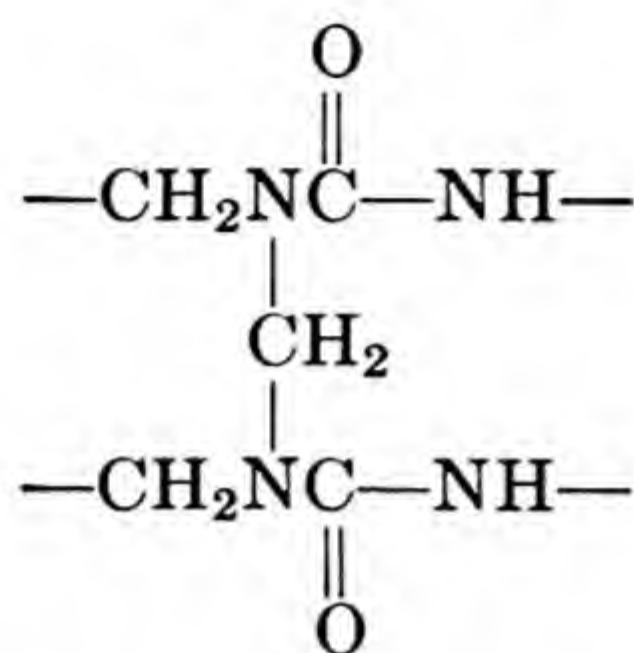
Production of the solid polymer results from reaction of the chain with more formaldehyde. Some of the —NH— groups add to formaldehyde forming —N— groups at points along the chain. When the



material is heated in a mold these groups react with free —NH— groups in adjacent chains. The chains thus become tied together, and the mol-

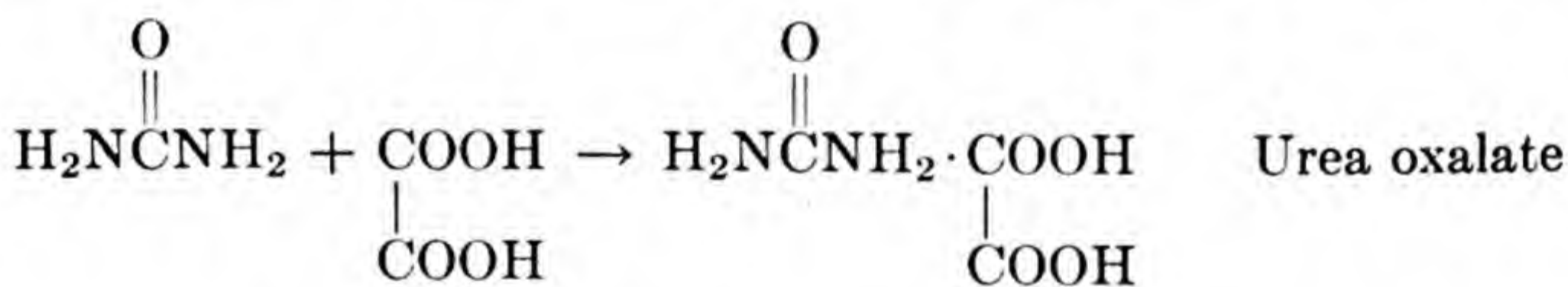
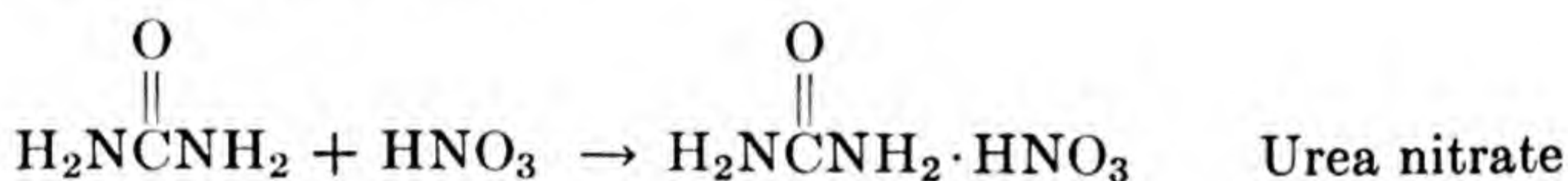


ecule is built up in three dimensions. The linking of the chains can be illustrated as follows.

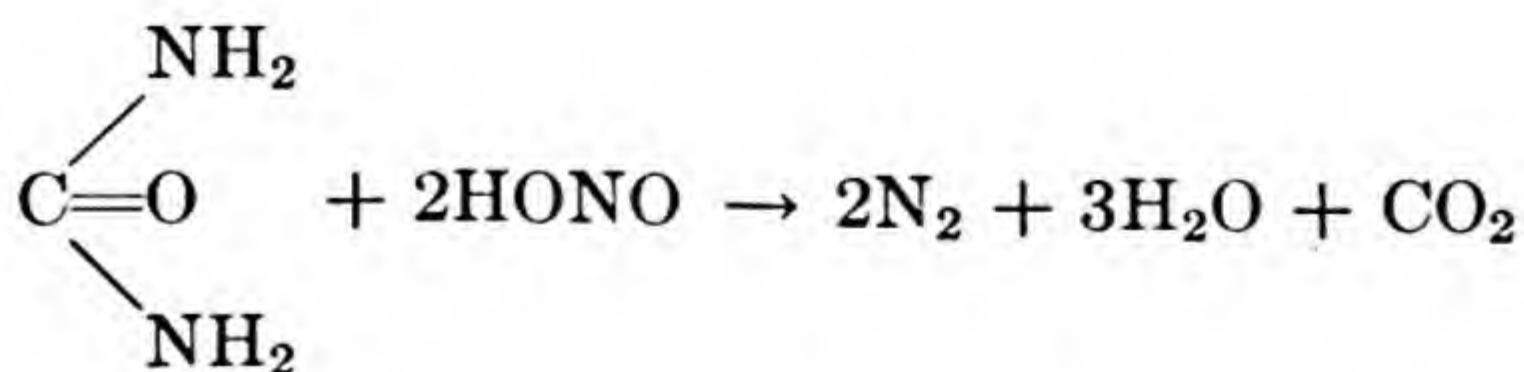
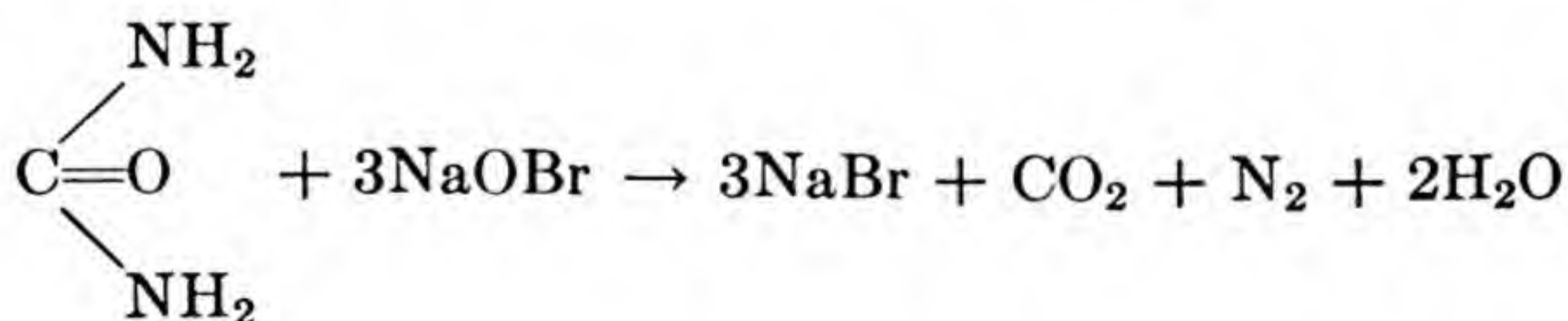


Since the polymer is formed by a condensation reaction, it is said to be a condensation polymer. When polymerization is accompanied by the linking together of long chains the polymer is cross-linked. Such materials are invariably less soluble and have higher softening points than the linear polymers. The plastic formed by condensation of urea and formaldehyde is sold as Beetleware or Plaskon. Urea-formaldehyde adhesives are also marketed. The material is applied as partially polymerized; heating or the use of a catalyst causes cross linking which produces a strong junction.

Urea is a weak base and with certain acids forms salts which can be used for its detection.

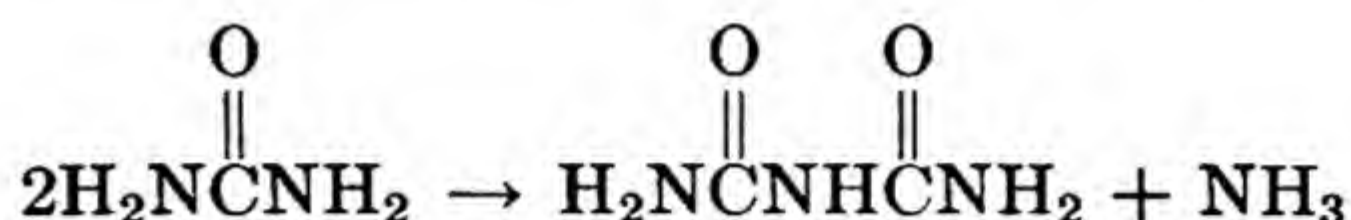


Urea can be determined quantitatively by measurement of the nitrogen evolved when it is treated with sodium hypobromite or nitrous acid.



It is also estimated quantitatively by the use of urease, an enzyme which occurs in certain types of beans. Urease hydrolyzes urea rapidly to carbon dioxide and ammonia; the ammonia can then be titrated with standard acid.

When urea is heated cautiously biuret is formed.

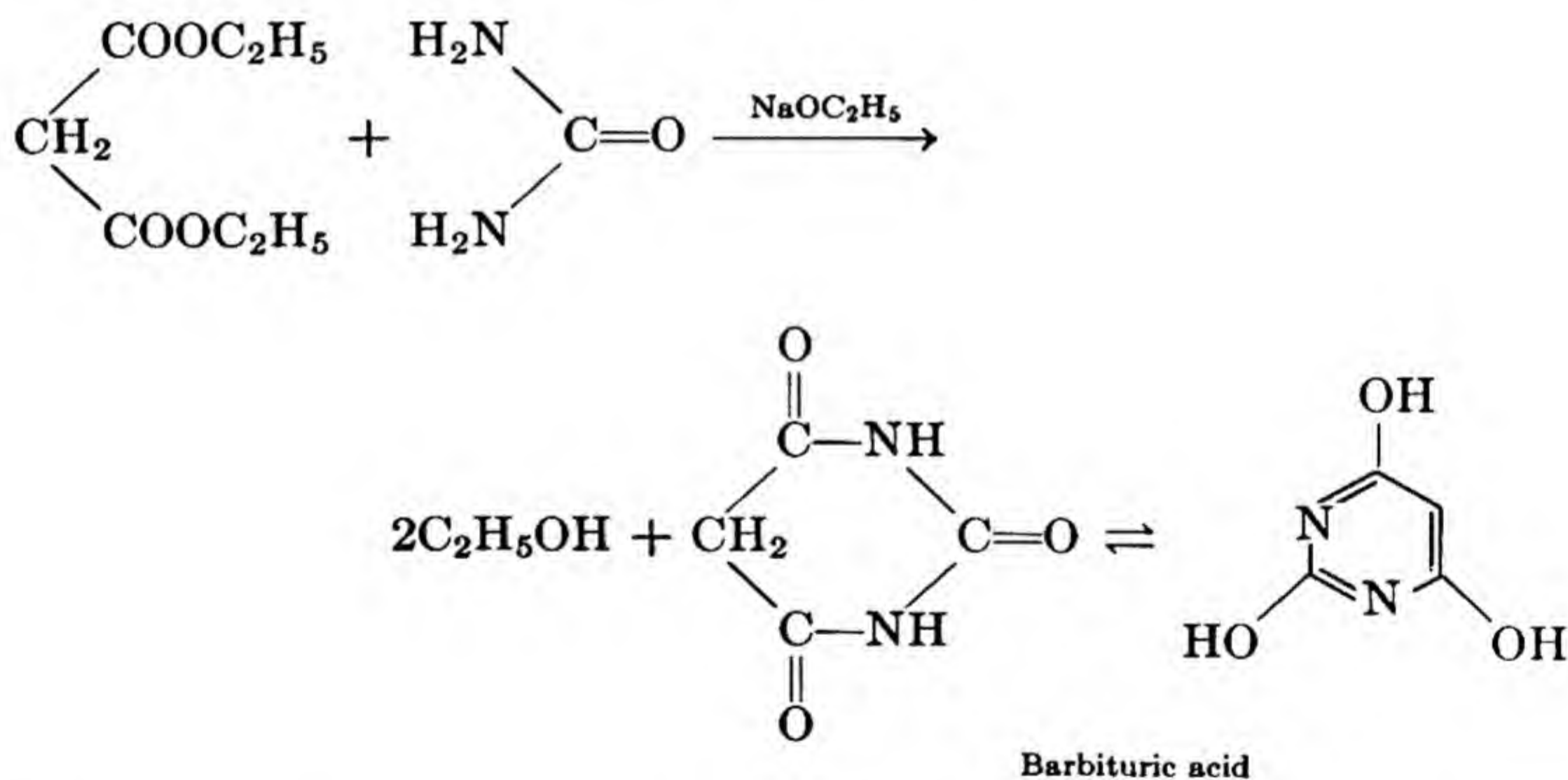


Biuret gives a violet color when treated with sodium hydroxide and cop-

per sulfate. Many substances with two or more  $-\overset{\text{O}}{\parallel}\text{C}-\text{NH}-$  linkages

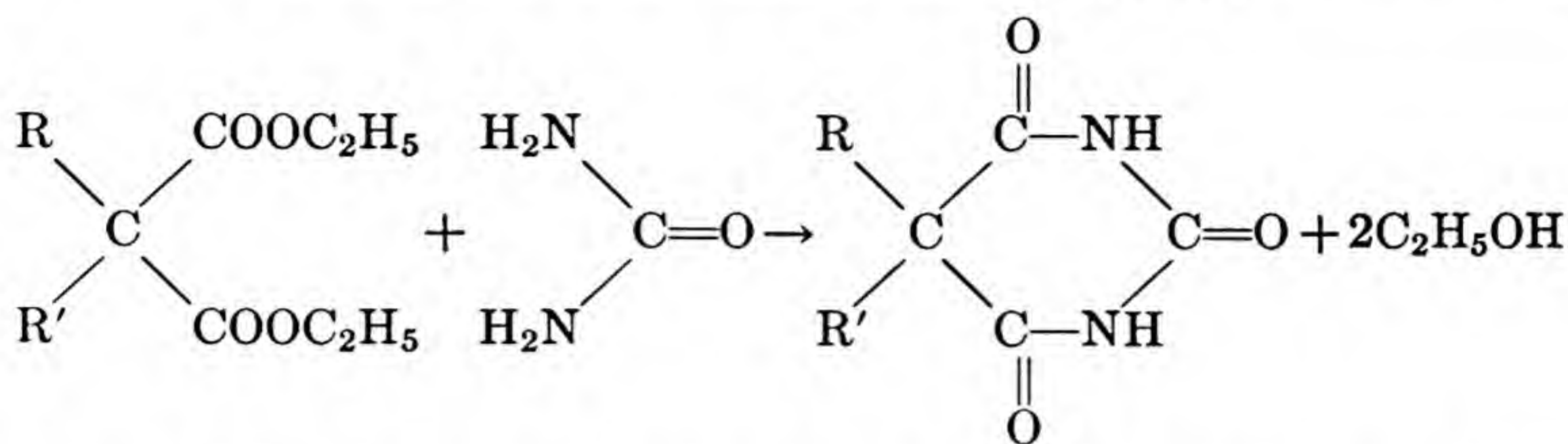
produce similar colors. This is known as the biuret test: it is often used with proteins.

When urea is treated with an ester of malonic acid under the appropriate conditions barbituric acid is formed.

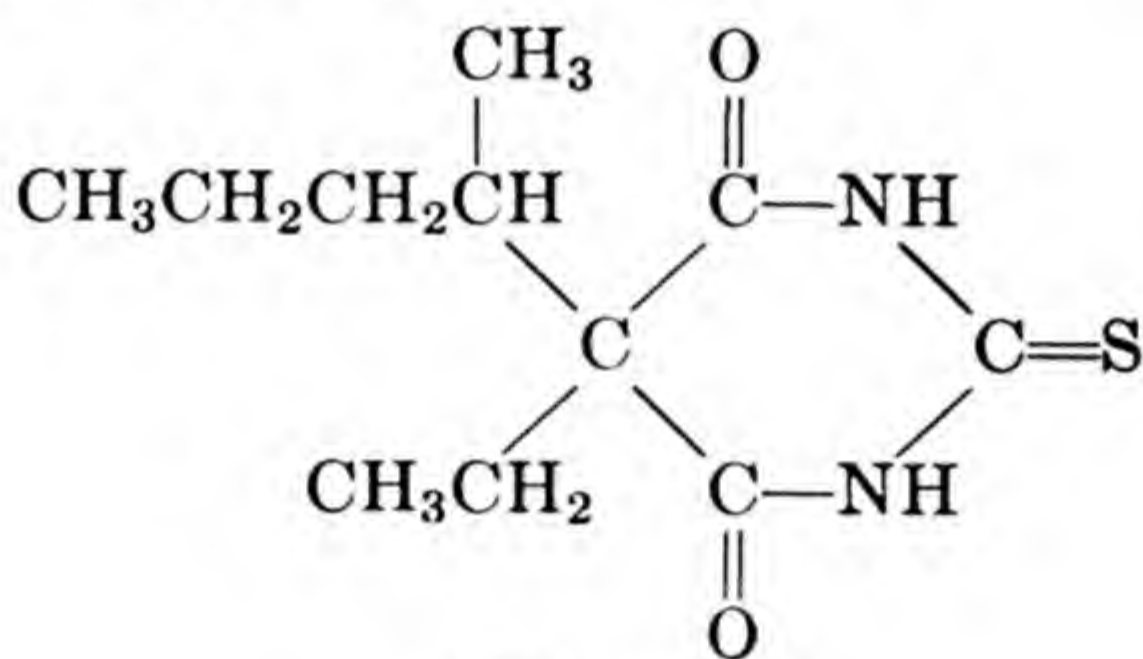


Solutions of barbituric acid behave as though both isomers were present in mobile equilibrium. Isomers like these, which readily undergo interconversion, are called *tautomers*. Substituted barbituric acids are sedatives; they are obtained from substituted malonic esters and urea.

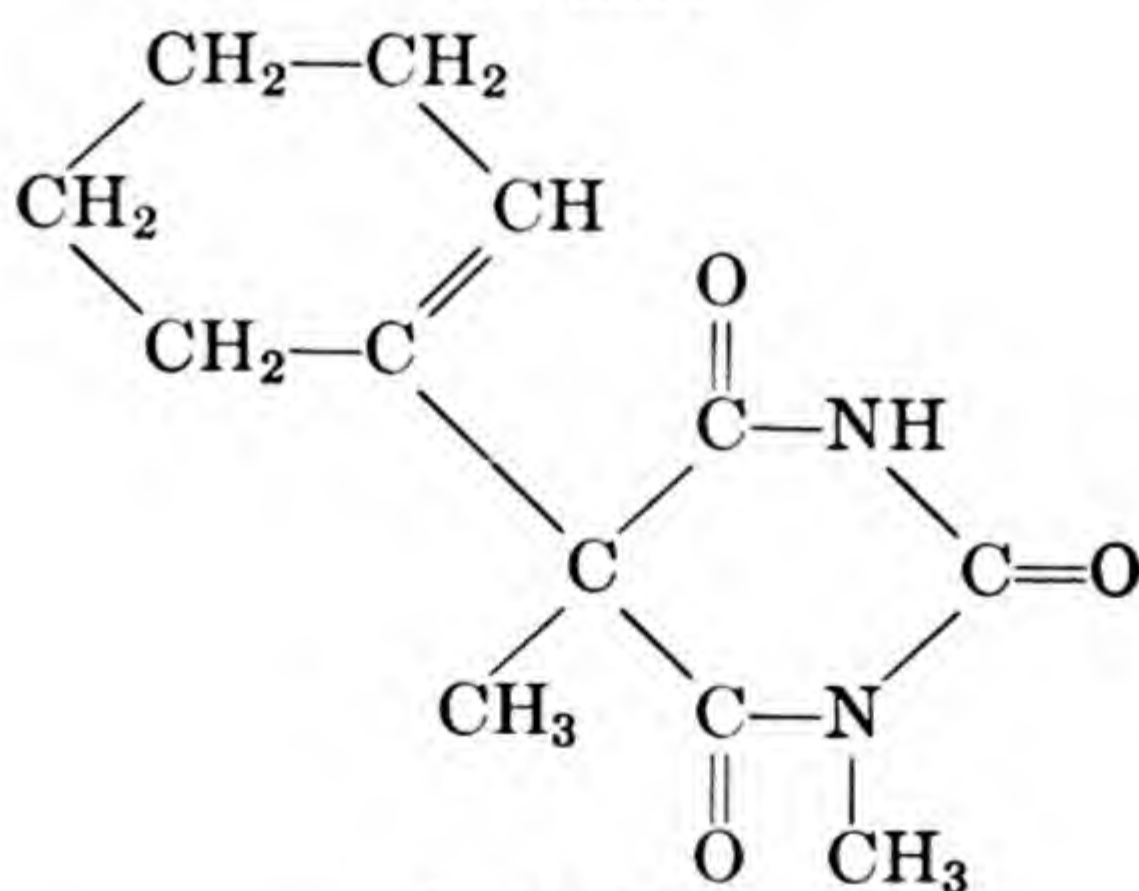




Several hundred substituted barbituric acids (barbiturates) have been prepared and tested, but only about twenty are employed clinically. Their —NH— groups have weakly acid properties, and thus the barbituric acids form salts. Solutions of the sodium salts of some of these compounds are employed as general anesthetics by injection. Though most barbiturates conform to the structure shown, certain modified compounds are also used clinically. For example, thiopental (Pentothal) is a thiobarbituric acid, and hexobarbital (Evipal) is an *N*-methylbarbituric acid.



Thiopental



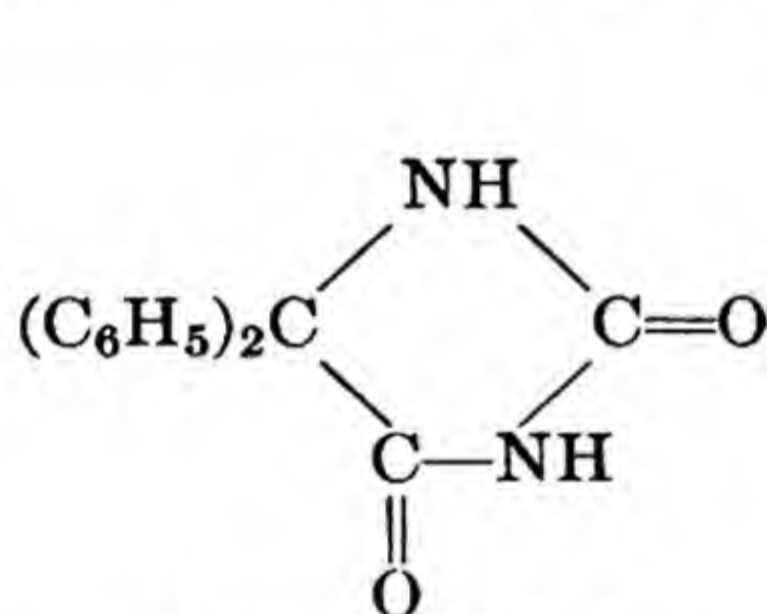
Hexobarbital

There is considerable variation in the duration of action of the barbiturates. Those of ultrashort action, such as hexobarbital, function for ten or fifteen minutes, whereas long acting drugs, such as phenobarbital, may function for two days. The table lists some of the commonly used barbiturates.

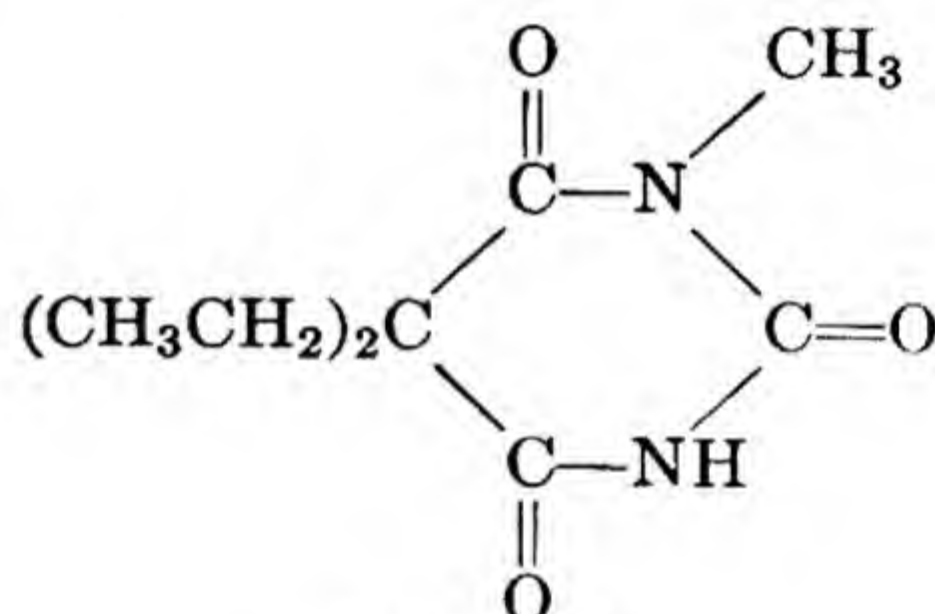
Generic (Proprietary) Name	R	R'
Amobarbital (Amytal)	Ethyl	Isoamyl
Barbital (Veronal)	Ethyl	Ethyl
Butabarbital (Butisol)	Ethyl	sec-Butyl
Phenobarbital (Luminal)	Ethyl	Phenyl
Pentobarbital (Nembutal)	Ethyl	2-Pentyl
Secobarbital (Seconal)	Allyl (CH <sub>2</sub> =CHCH <sub>2</sub> —)	2-Pentyl

Barbiturates, like many central nervous system depressants, can be habit forming if they are taken consistently over a period of time. Large and frequent doses of these agents may produce tolerance to their action, so that still larger doses may be required for a given effect.

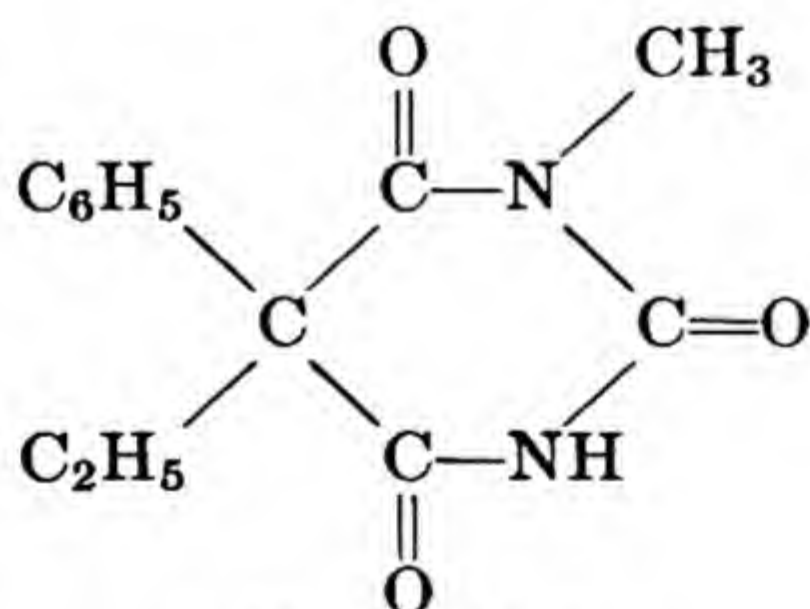
Certain derivatives of urea and some other closely related compounds have been successfully applied in the inhibition of epileptic seizures. Compounds with this quality are called anticonvulsants. Phenobarbital is used for this purpose; the structures of other anticonvulsants are given below.



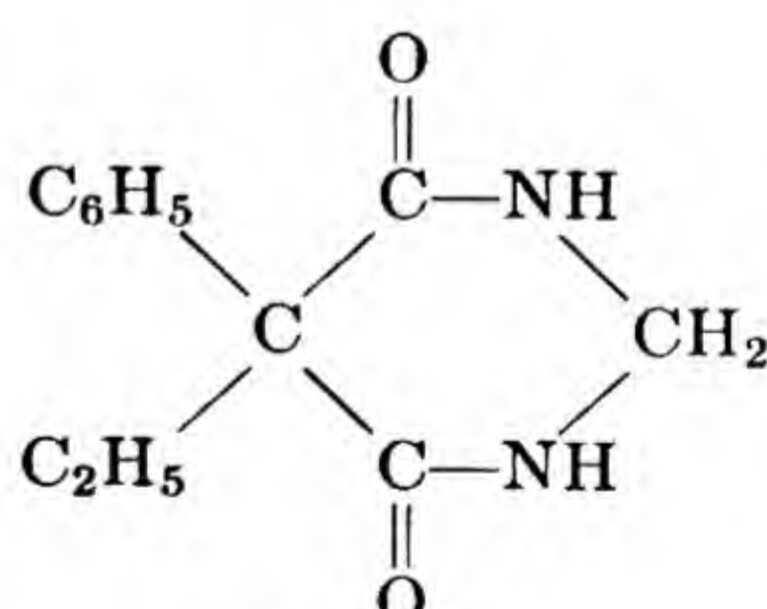
5,5-Diphenylhydantoin  
(Dilantin)



Metharbital



Mephobarbital

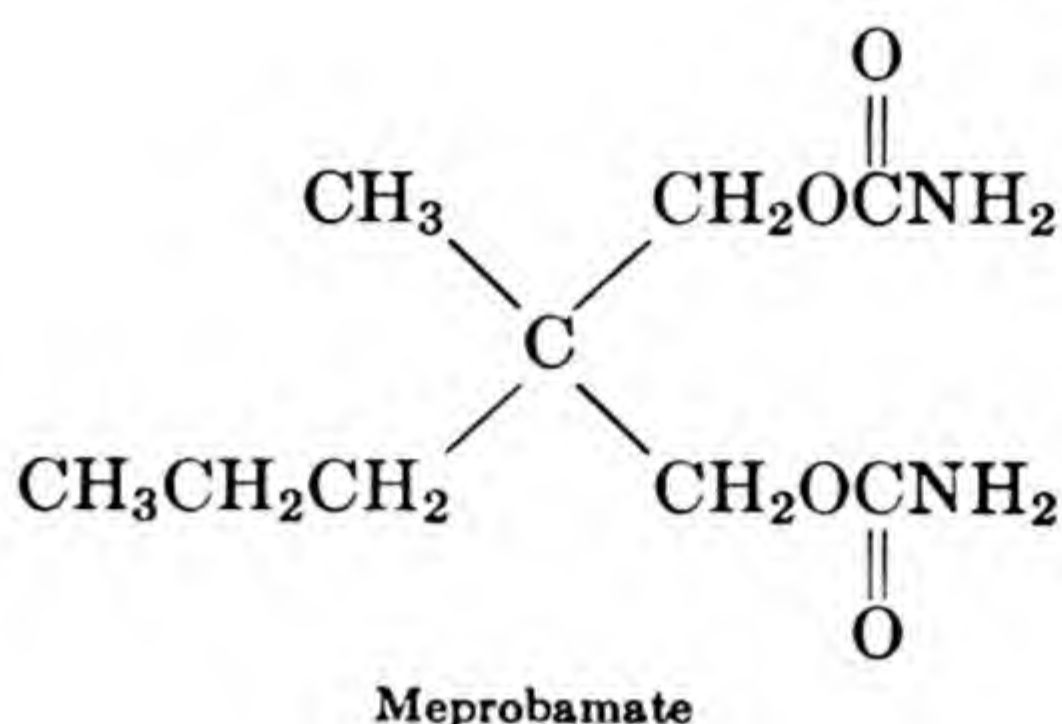
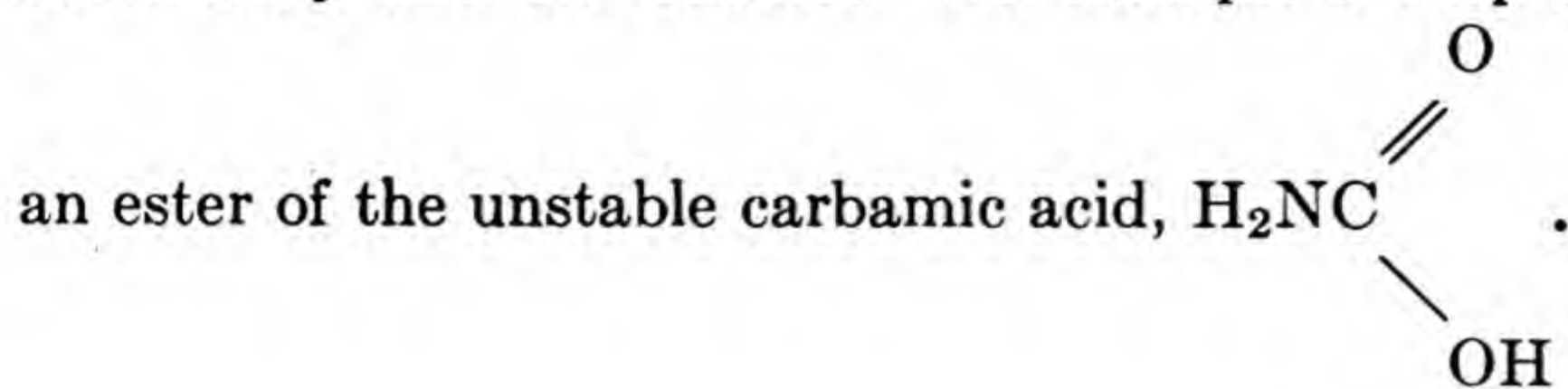


Primidone  
(Mysoline)

Tranquilizers are a more recent development than sedatives. They are widely employed in the therapy of mental illness, in which they have proved of great worth. They are valuable also in cases of hyper-

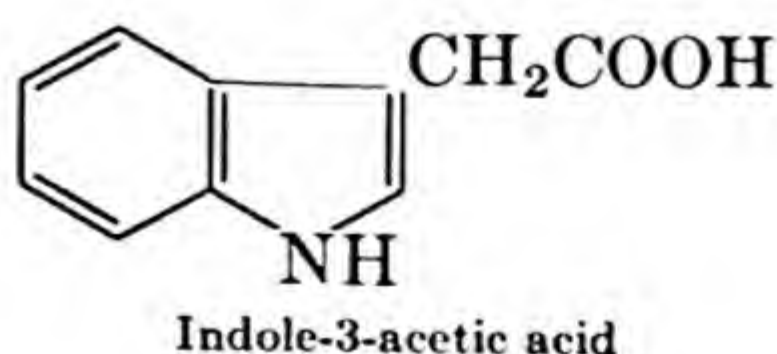
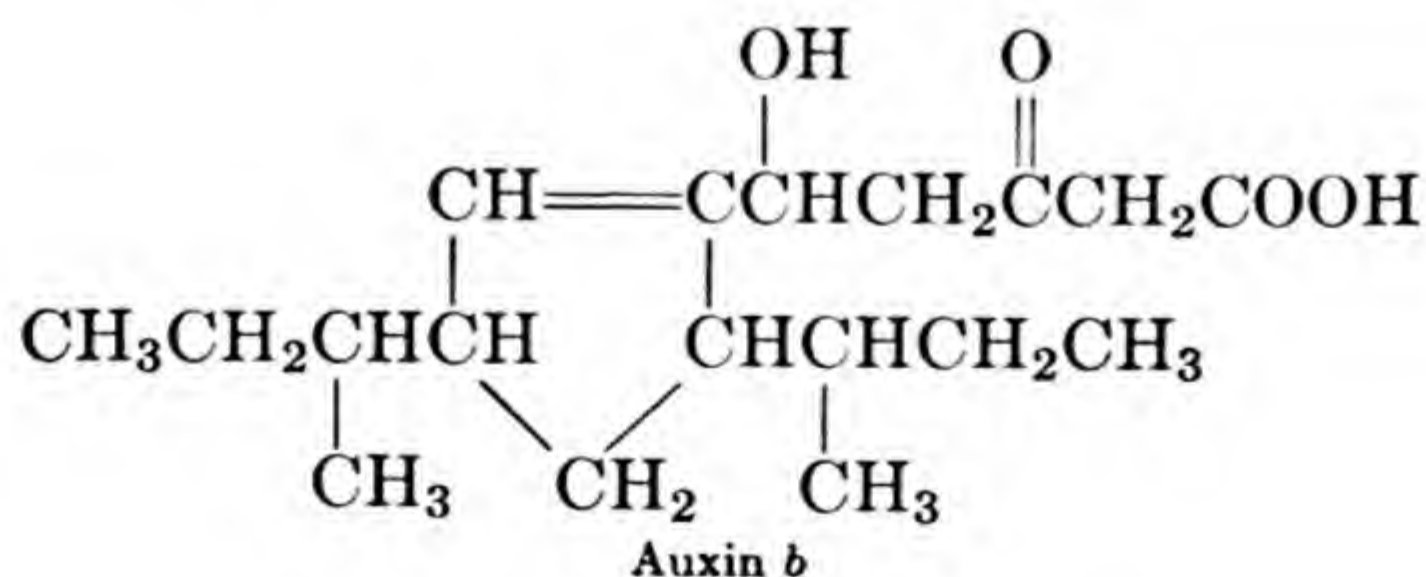
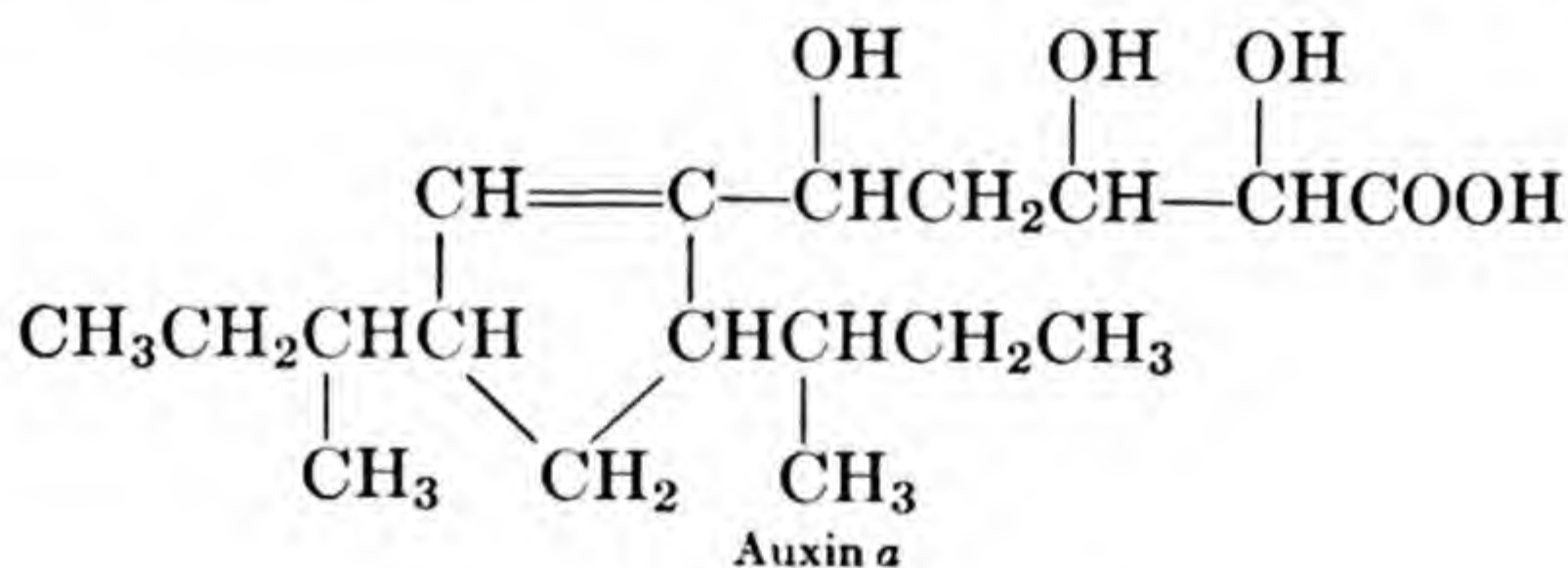


excitability and nervousness. An example is meprobamate, which is

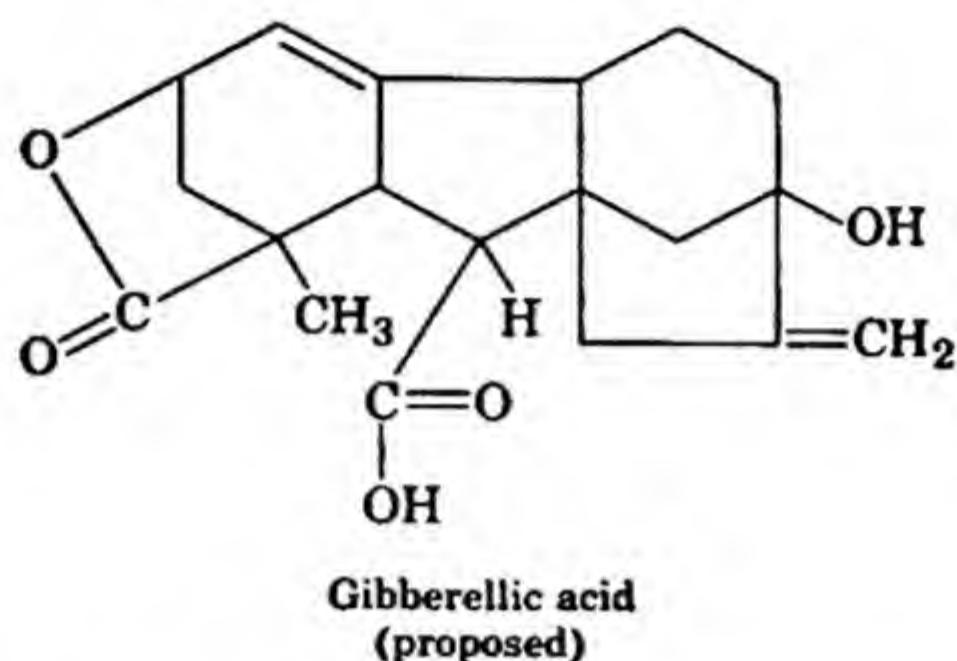


## ► PLANT HORMONES

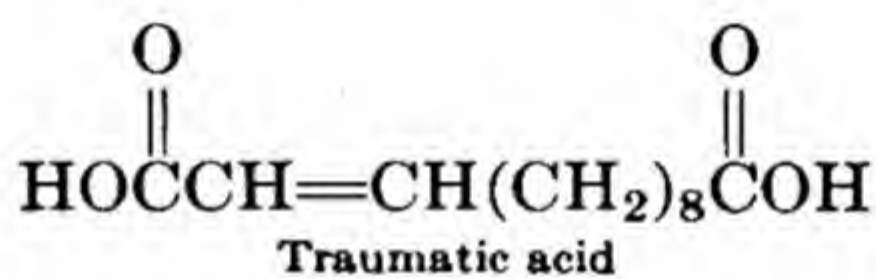
A number of substances, auxin *a*, auxin *b*, and indole-3-acetic acid, function as growth hormones in plants. They act by encouraging cell division and elongation. They also induce the formation of new roots. Certain synthetic substances, such as indole-3-butyric acid



and a number of aryloxyacetic acids,  $\text{ArOCH}_2\text{COOH}$ , have similar effects. They may accelerate growth to such an extent that they can cause the death of the plant; therefore they are used as herbicides (Chapter 16). Another substance having the properties of a plant hormone is gibberellic acid, which accelerates the growth of many plants. It is isolated from a fungus.

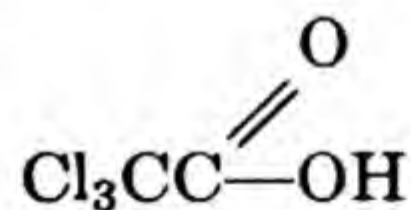


When a plant is injured scar tissue grows over the wound. A compound known to be concerned with the growth of scar tissue in some plants is traumatic acid.

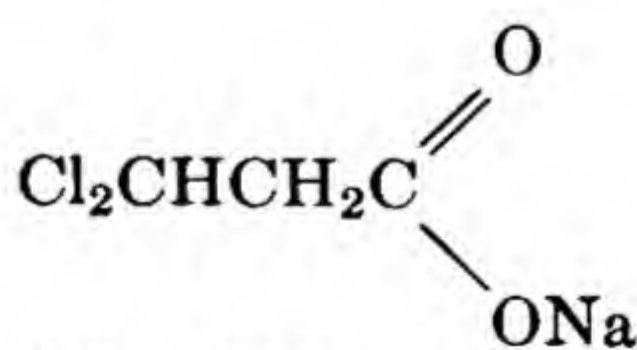


## ► HERBICIDES

Herbicides are substances used to control the growth of undesirable plants (weeds) which cause great loss to agriculture because they remove nutrients and water from the soil. Herbicides may be applied to the soil before growth has occurred (pre-emergence type) or directly to the plant. They are, for the most part, acids or derivatives of acids. For example, trichloroacetic acid is valuable in killing perennial grasses, and sodium dichloropropionate has a similar usefulness.



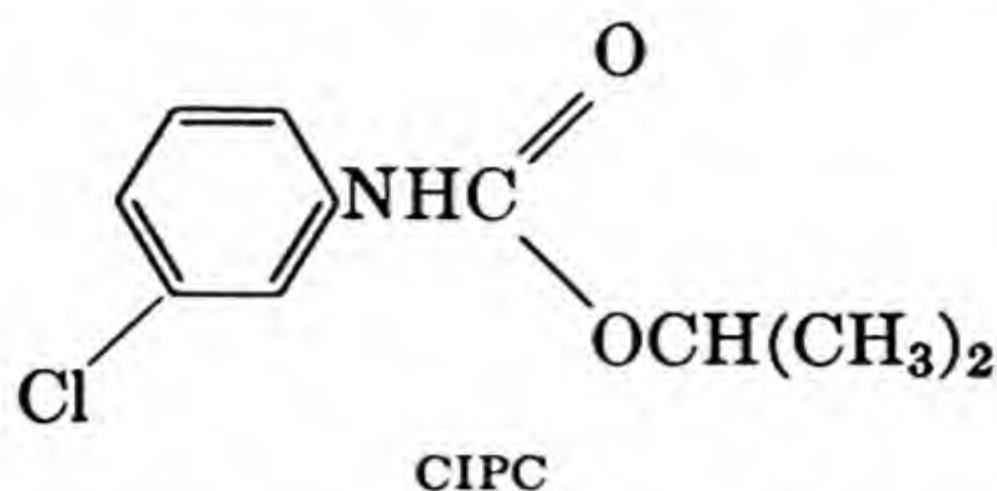
Trichloroacetic acid



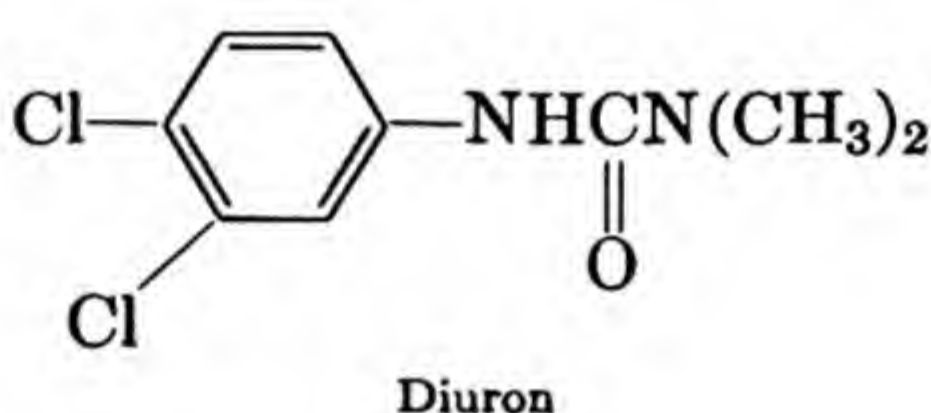
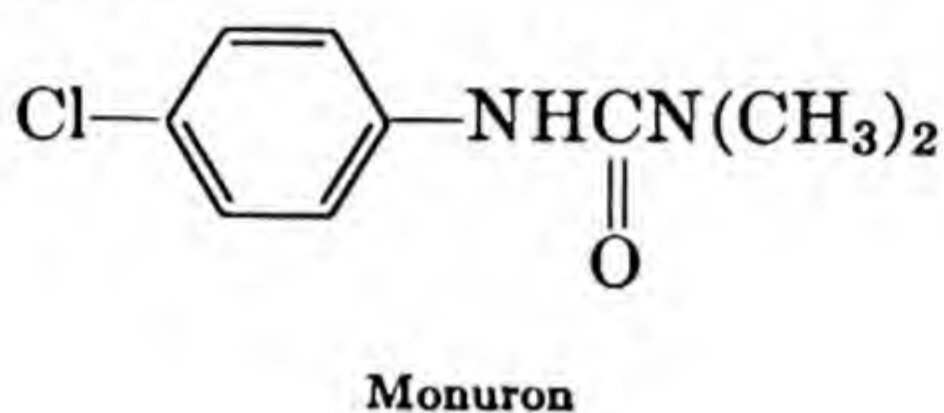
Sodium dichloropropionate  
(Radapon)

Some structurally more complex herbicides are 2,4-D, 2,4,5-T (see Chapter 16), and CIPC, isopropyl *N*-(*m*-chlorophenyl)carbamate, a pre-emergence herbicide for cotton and vegetable crops.





Frequently it is desirable to prevent plant growth entirely in locations where mowing is impractical, as, for example, in ditches and along railroad rights-of-way. For this purpose certain substituted ureas have proved useful. Examples are 3-*p*-chlorophenyl-1,1-dimethylurea (monuron) and 3-(3,4-dichlorophenyl)-1,1-dimethylurea (diuron).



## ► QUESTIONS

1. Write equations for the following reactions:

- Acetic acid +  $\text{SOCl}_2 \rightarrow$
- Furoic acid +  $\text{NaHCO}_3 \rightarrow$
- n*-Butyramide +  $\text{H}_2\text{O} \xrightarrow{\text{HCl}}$
- Ethyl benzoate +  $\text{NH}_3 \rightarrow$
- Phthalic acid + ethyl alcohol  $\rightarrow$
- Dimethylmalonic acid, heated  $\rightarrow$
- Phosgene + methanol  $\rightarrow$
- Ammonium formate, heated  $\rightarrow$
- Ethyl propionate +  $\text{LiAlH}_4 \rightarrow$
- Acetic anhydride + ethanol  $\rightarrow$

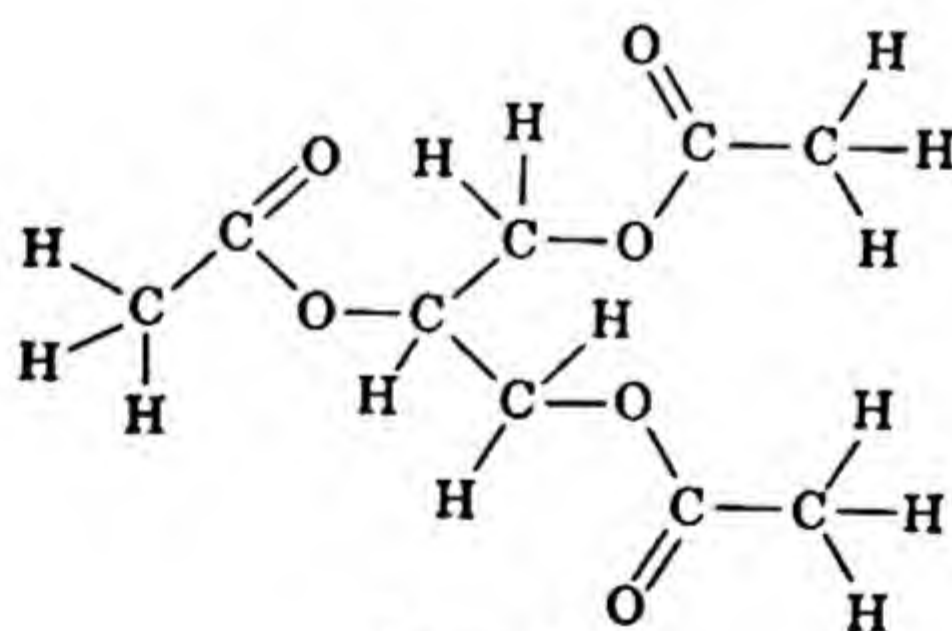
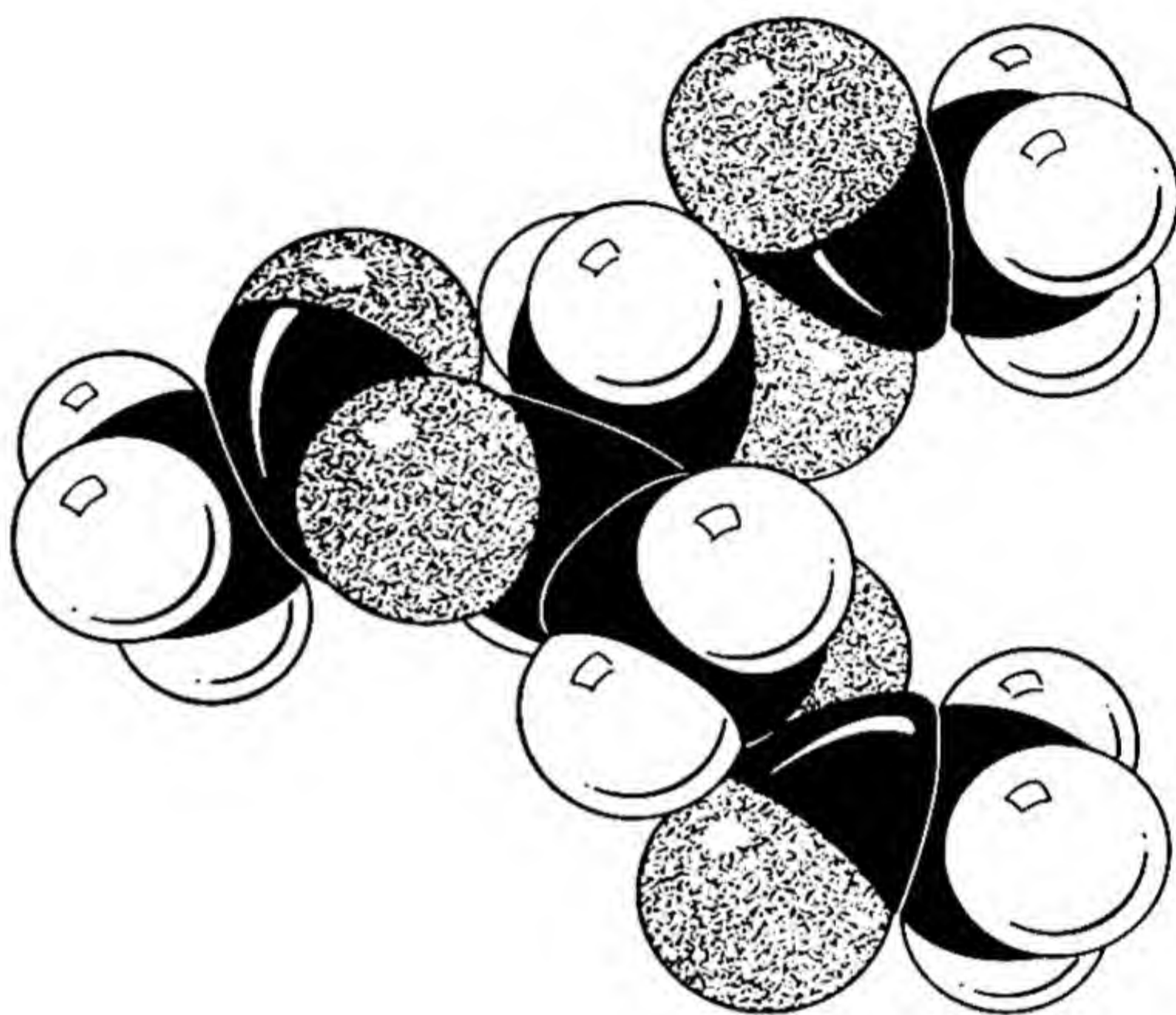
2. Show by equations how *n*-butyryl chloride would behave when treated with the following compounds under appropriate conditions: (a) water, (b) methanol, (c) sodium acetate, (d) ammonia.

3. Glycerol esters of isovaleric acid,  $(\text{CH}_3)_2\text{CHCH}_2\text{C} \begin{array}{l} \nearrow \text{O} \\ \searrow \text{OH} \end{array}$ , occur in por-

poise oil. Would you expect that this acid would be of widespread natural occurrence? Explain.

4. List the classes of compound mentioned in this chapter that react with ammonia. Show the equations for these reactions.

# Naturally occurring esters



Triacetin

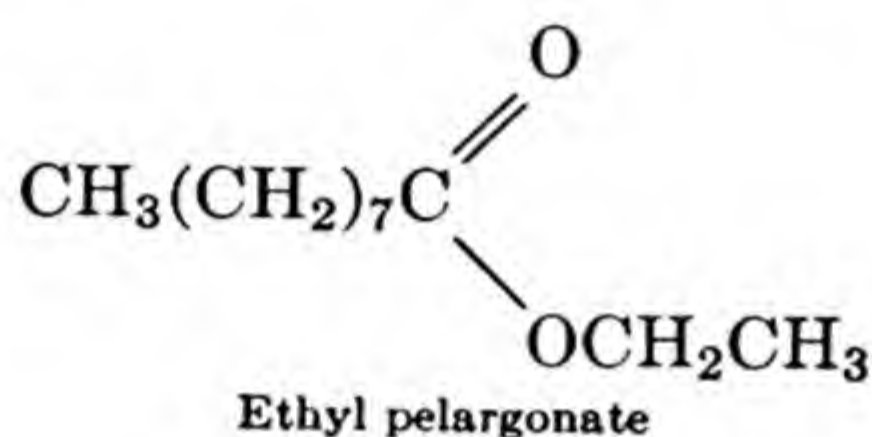
Though triacetin is not found in nature, its homologs occur widely in fats and vegetable oils. The naturally occurring glycerides are derivatives of acids of high molecular weight, most of them having twelve or more carbon atoms. A model of such a compound would have long chains in place of the methyl groups in triacetin.



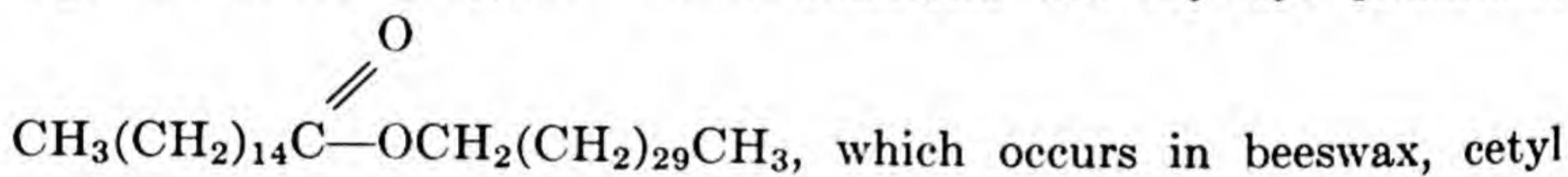
▶ **ESSENTIAL OILS**

The flowers, leaves, fruit, and other portions of plants often contain mixtures of organic materials called essential oils, many of which have distinctive odors. Frequently several classes of compounds are present. A few esters which have been isolated from essential oils are given in the following table.

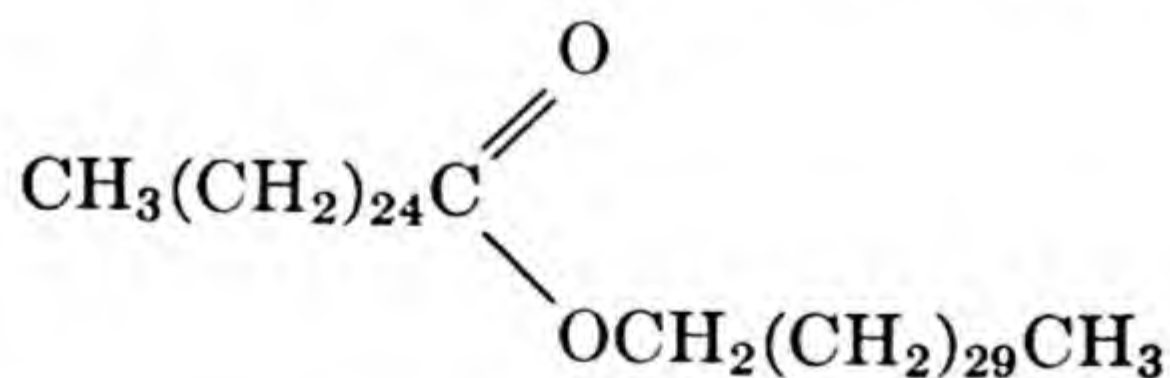
Fruit flavors are complex mixtures, mostly purely aliphatic esters. Artificial fruit flavors are also mixtures of esters. Thus ethyl *n*-butyrate is a constituent of pineapple flavors, isoamyl acetate of banana, ethyl isovalerate of raspberry and peach, and ethyl pelargonate of quince.

▶ **WAXES**

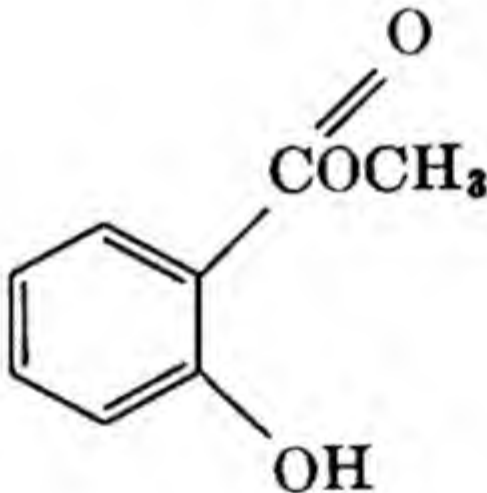
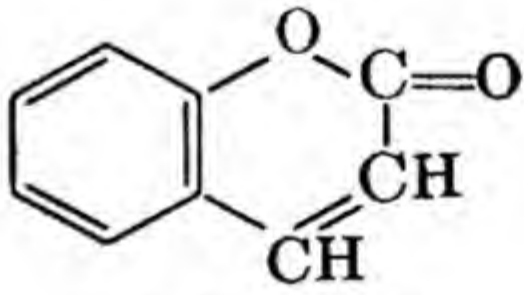
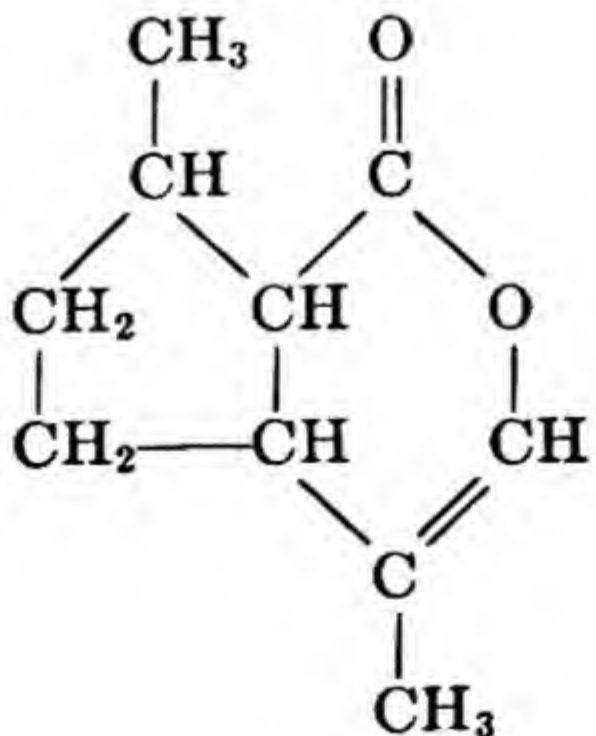
Naturally occurring waxes are solids having a greasy feel. They may contain esters, alcohols, acids, or hydrocarbons, but the esters predominate in many examples. They are simple in type but have high molecular weights. Some examples are myricyl palmitate,



palmitate,  $\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_3(\text{CH}_2)_{14}\text{C} \end{array} \text{—OCH}_2(\text{CH}_2)_{14}\text{CH}_3$ , which is found in spermaceti, from the sperm whale, and myricyl cerotate



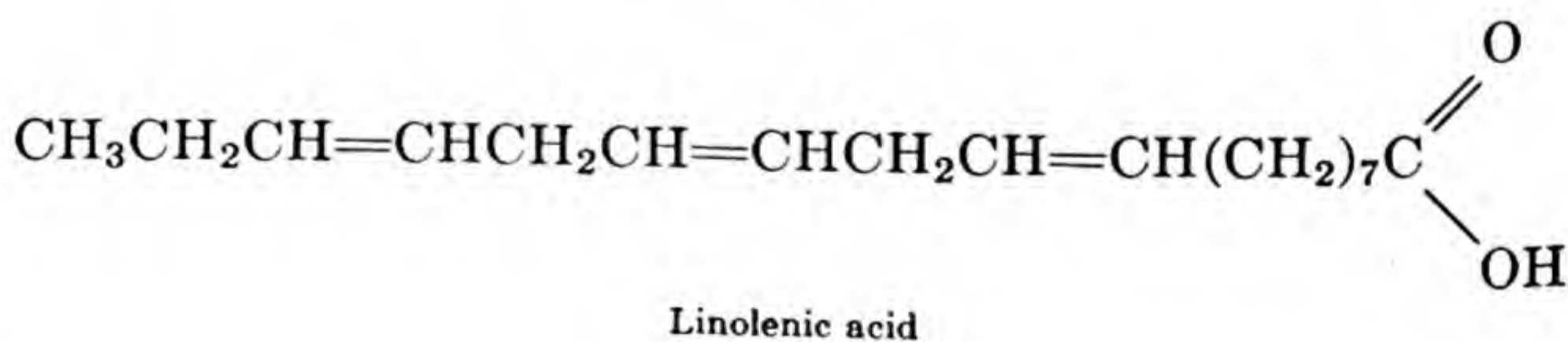
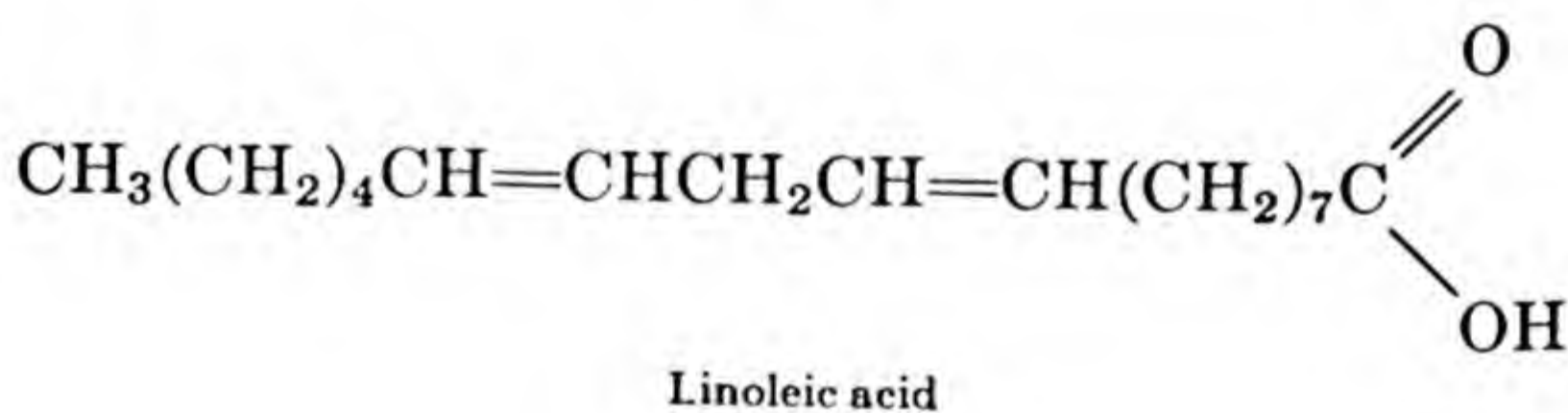
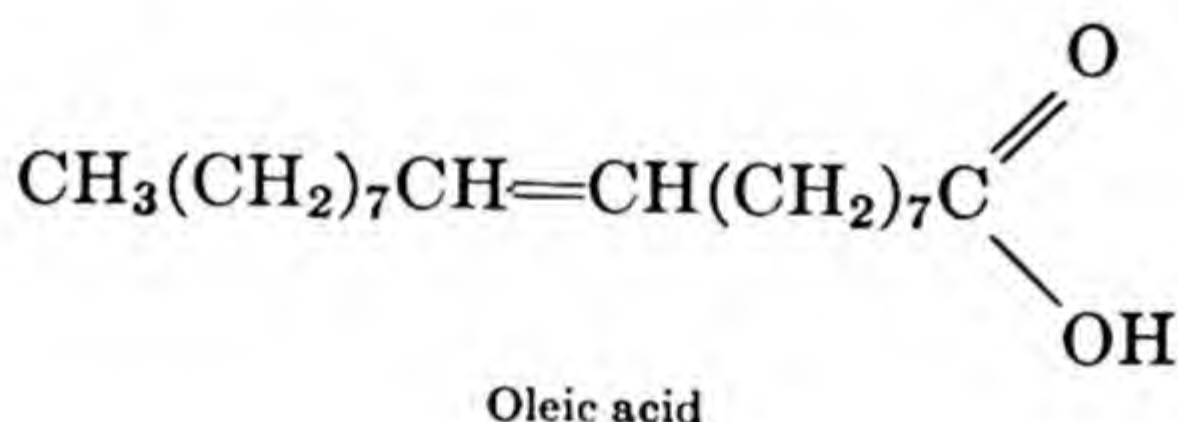
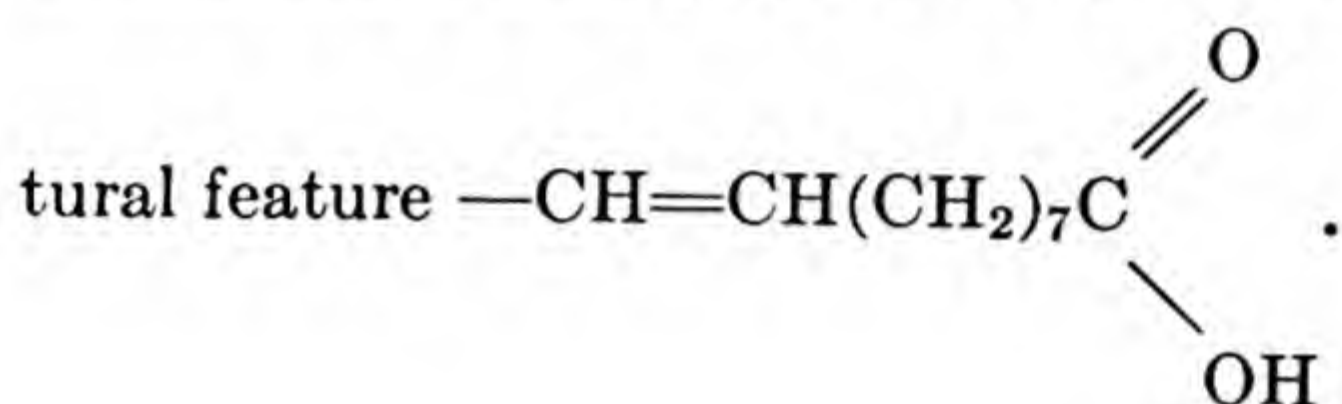
in carnauba wax, obtained from the leaves of a palm tree that grows in South America.

Ester	Formula	Occurrence
Ethyl <i>n</i> -butyrate	$\text{CH}_3\text{CH}_2\text{CH}_2\text{C} \begin{array}{l} \text{O} \\ \parallel \\ \text{OCH}_2\text{CH}_3 \end{array}$	Pineapples
Isoamyl acetate	$\text{CH}_3\text{C} \begin{array}{l} \text{O} \\ \parallel \\ \text{OCH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2 \end{array}$	Pears
Isoamyl isovalerate	$(\text{CH}_3)_2\text{CHCH}_2\text{C} \begin{array}{l} \text{O} \\ \parallel \\ \text{OCH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2 \end{array}$	Bananas
Benzyl acetate	$\text{CH}_3\text{C} \begin{array}{l} \text{O} \\ \parallel \\ \text{OCH}_2\text{C}_6\text{H}_5 \end{array}$	Jasmine
Methyl benzoate	$\text{C}_6\text{H}_5\text{C} \begin{array}{l} \text{O} \\ \parallel \\ \text{OCH}_3 \end{array}$	Tuberoses
Methyl salicylate		Wintergreen
Coumarin		Tonka beans, hay
Nepetalactone		Catnip

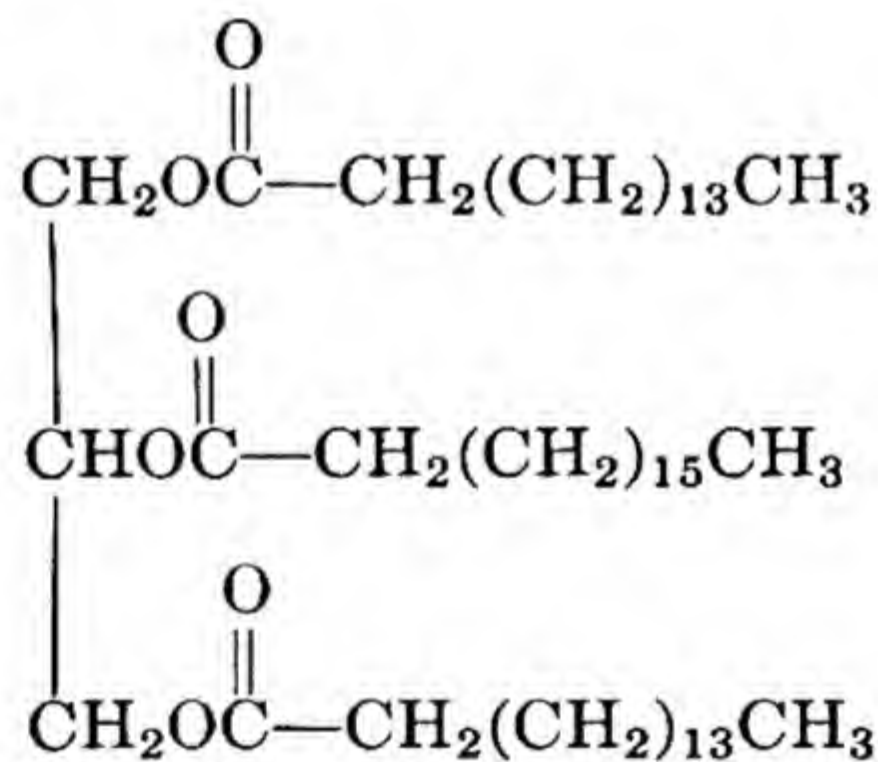
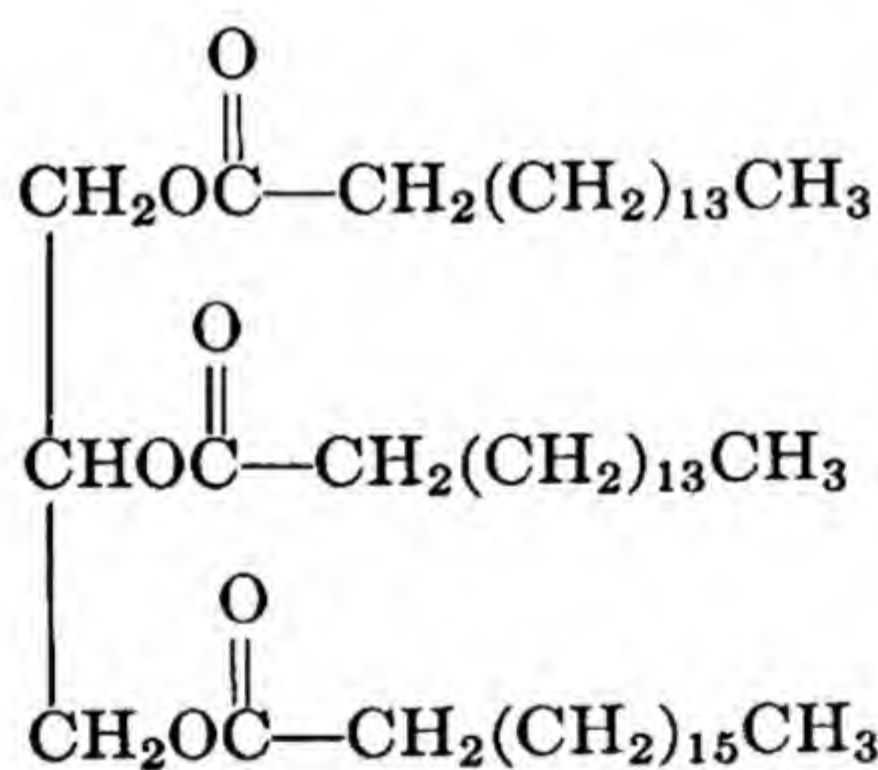
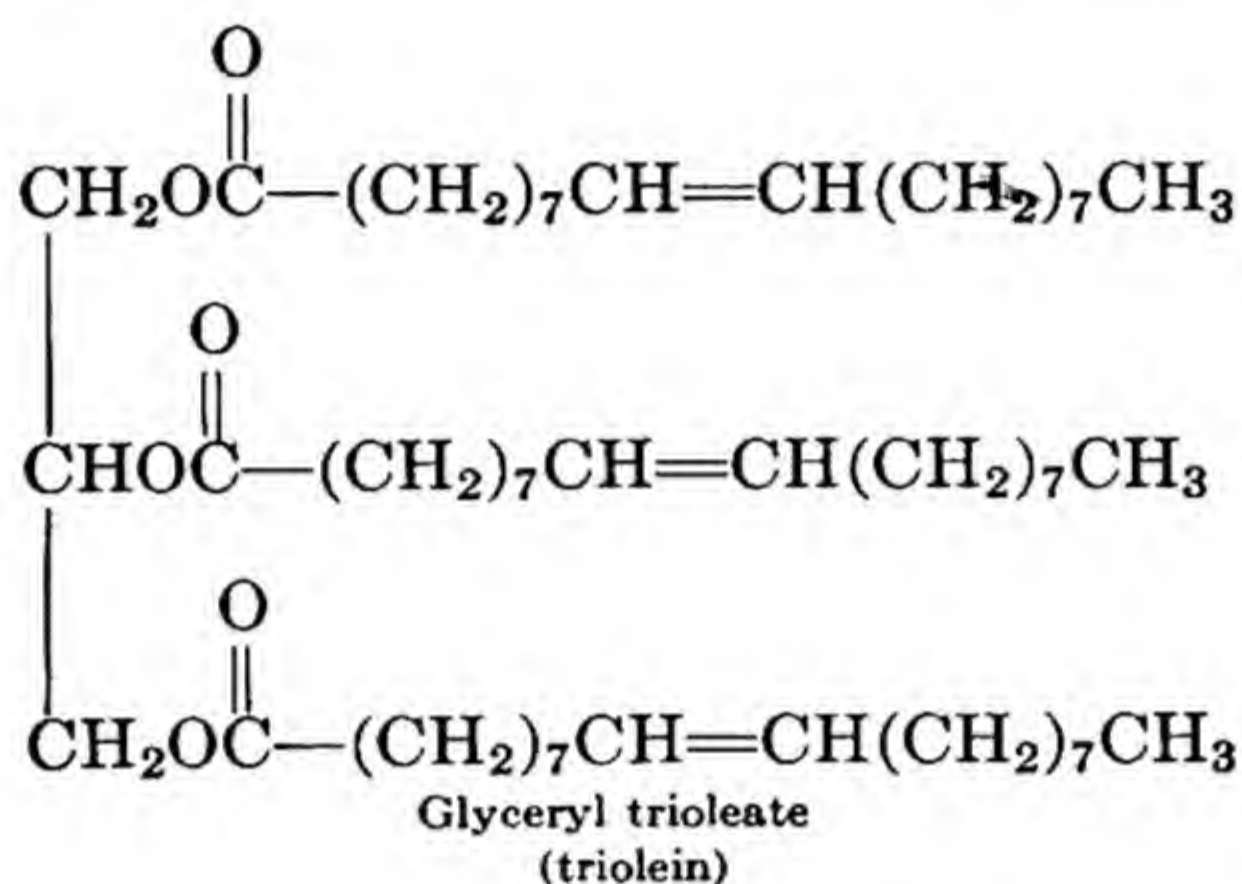
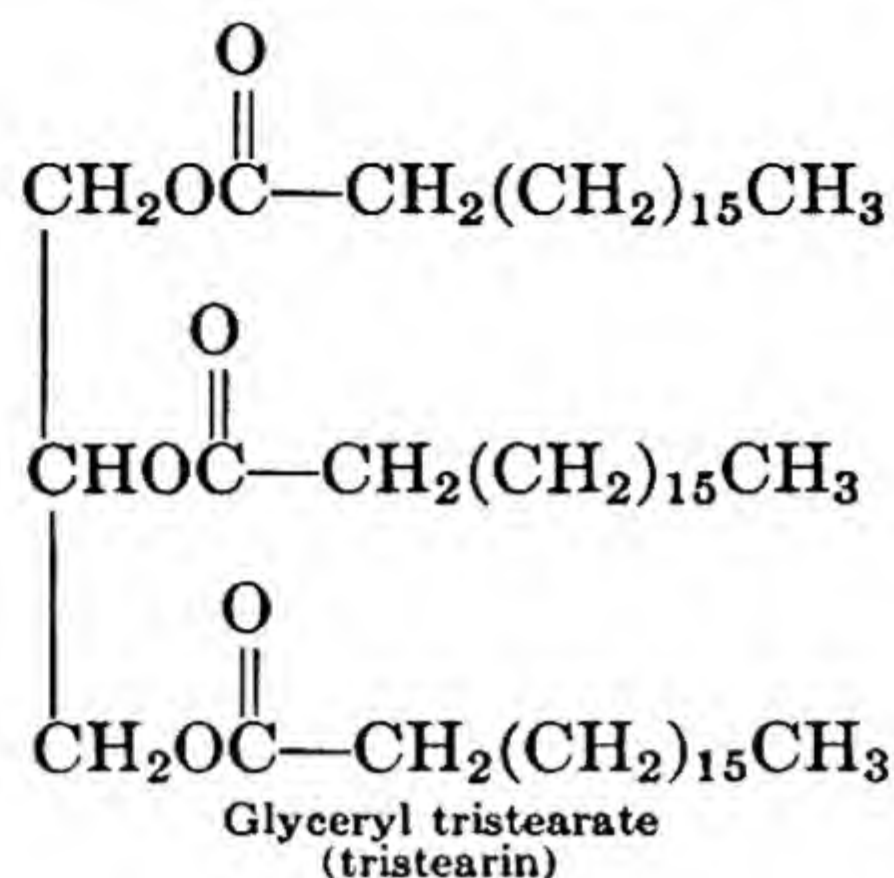
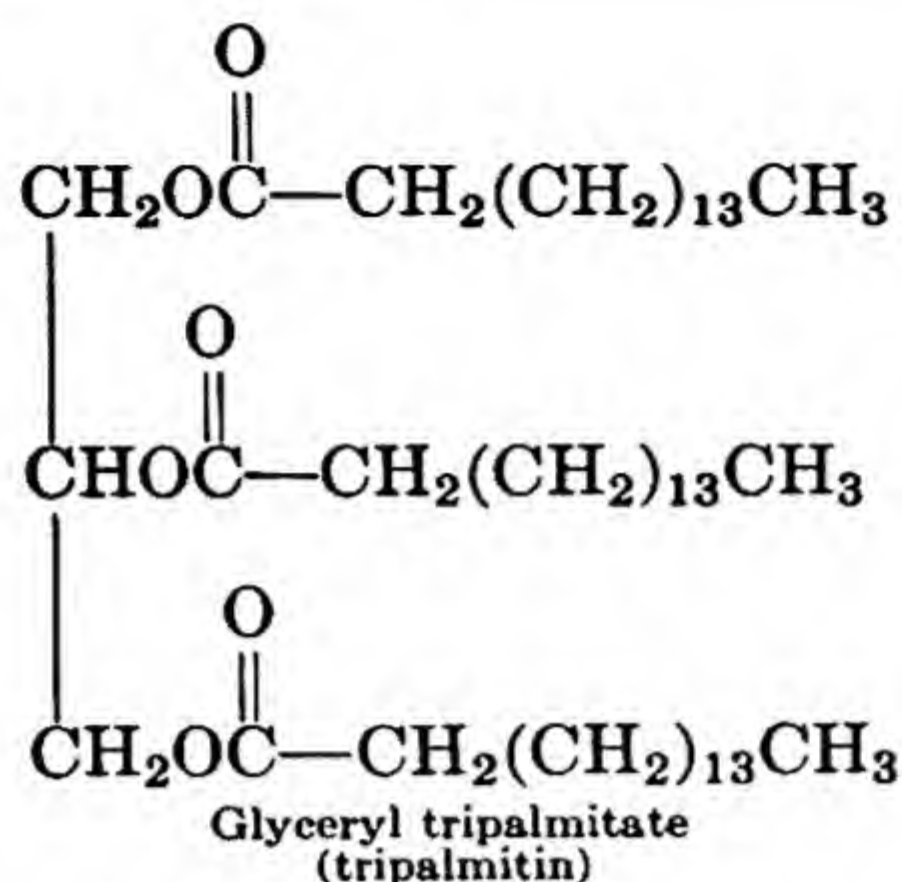


► **FATS AND OILS**

Animal fats (such as lard, butter, and tallow) and animal and vegetable oils (such as olive oil, linseed oil, cottonseed oil, and cod-liver oil) possess properties which show them to be esters. Saponification converts them into soaps and glycerol, a trihydroxy alcohol. Soaps are salts of acids of high molecular weight; it follows that fats and oils are esters of glycerol with these acids. Such compounds are known as glycerides. If the soaps are acidified, a mixture of acids, sometimes very complex, is obtained. Saturated acids, mostly of high molecular weight, such as stearic and palmitic acids, and unsaturated acids, such as oleic, linoleic, and linolenic acids are present. These three unsaturated acids have eighteen carbon atoms and possess the common struc-



Evidence indicates that in the fat or oil there are present not only simple glycerides, involving only one kind of acid group, but also more complex molecules having two or three different acid groups. In a fat which gives stearic, palmitic, and oleic acids on hydrolysis the following glycerides, among others, might be present.

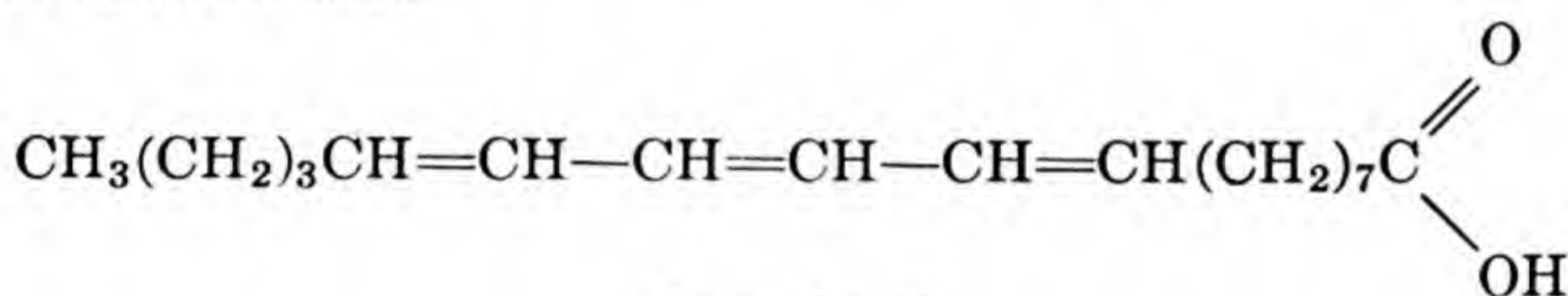


Stearodipalmitins

In addition, two oleodipalmitins and two oleodistearins as well as three glycerides containing all three acid residues are possible. In all there could be eighteen glycerides possibly present in the original fat. When it is realized that the mixture of acids from the hydrolysis of a fat or oil usually contains more than three acids it is readily seen that the natural fats and oils are of exceptional complexity. Butterfat is an outstanding example: fourteen different acids have been shown to be present, so that the number of possible glycerides in butter is enormous.



The consistency of a fat or oil depends upon its composition. The presence of unsaturation tends to lower the melting point; therefore oils are usually more unsaturated than fats. The presence of fatty acids of low molecular weight also tends to lower the melting point. The consistency of butterfat is due in part to this phenomenon. Another example is coconut oil, which contains very little unsaturation but much trilaurin. The amount of unsaturation in a fat or oil is usually expressed in terms of its iodine number, which is defined as the weight in grams of iodine which reacts with 100 grams of fat or oil. (The reagent actually used is iodine chloride, ICl, or iodine bromide, IBr.) Thus the more highly unsaturated oils have higher iodine numbers. Oils are often divided into three categories, depending upon their behavior when spread in a thin film and exposed to the air. *Drying oils*, such as linseed oil and tung oil, first become sticky and later form dry, tough, cohesive films. *Semidrying oils*, such as cottonseed oil and peanut oil, become sticky but do not dry. *Non-drying oils* do neither. The drying process involves oxidation and polymerization and is associated with the double bonds in the oil. Thus tung and linseed oils contain large amounts of unsaturated fatty acid esters. Tung oil contains esters of eleostearic acid, an isomer of linolenic acid.



Eleostearic acid

The following table shows the composition of the fatty-acid mixtures from various fats and oils and its relation to the iodine number.

Fat or Oil	Iodine Number	Acids (%)							
		Lau-ric	My-ris-tic	Pal-mitic	Ste-aric	Oleic	Lin-oleic	Lino-lenic	Eleo-ste-aric
Coconut oil	8-10	48	17	8	2	6	2		
Beef tallow	30-50		2	32	15	48	3		
Lard	45-65		1	30	18	41	6		
Olive oil	80-85			6	4	83	7		
Peanut oil	85-90			7	5	60	21		
Cottonseed oil	100-110			21	2	33	43		
Corn oil	115-130			7	3	46	42		
Soybean oil	125-135			6	4	33	53		
Tung oil	160-180			4	1	15			80
Linseed oil	170-200			5	3	5	62	25	

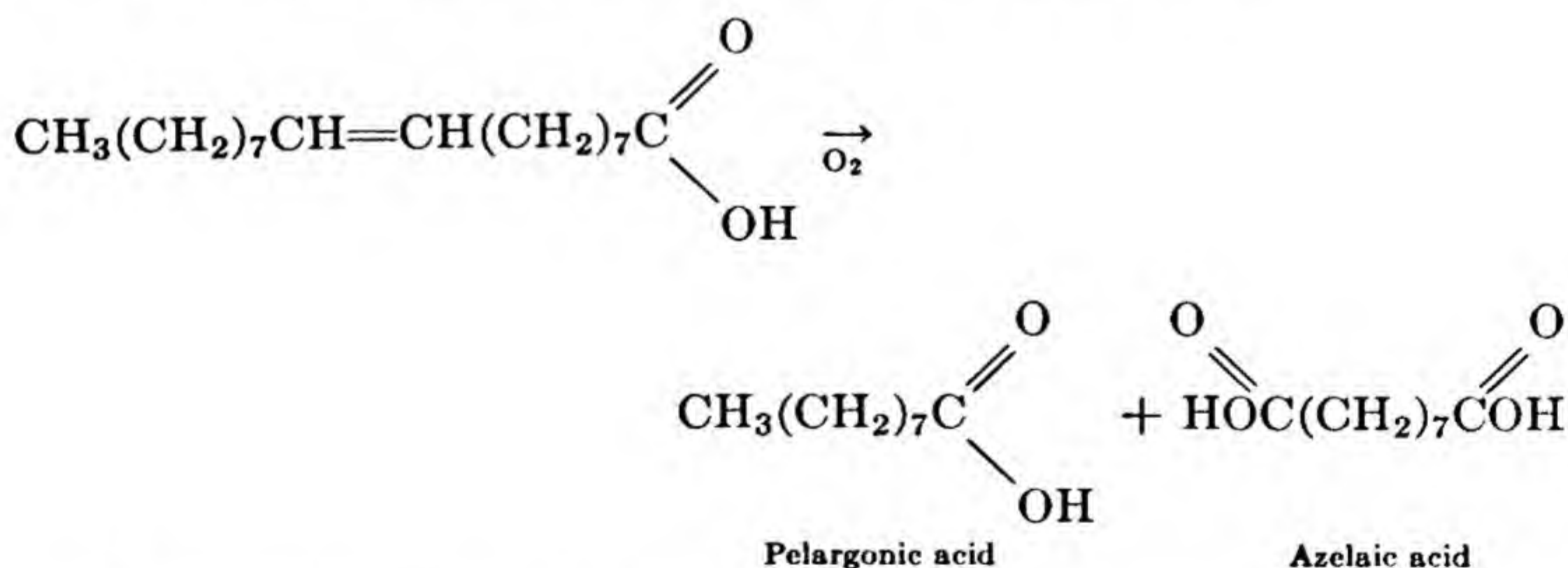


Fats and oils show variation in composition, depending upon species and strain differences, the time of the year, and the type of food used by the organism.

The drying oils are employed in paints. The tough film resulting from the drying process affords good protection to the surface against deterioration caused by the sun and atmospheric elements. In addition to the drying oil, paints also contain a catalyst, usually a cobalt salt, which speeds up the drying process, a pigment, usually a finely divided inorganic substance, and a thinner, such as turpentine, which lowers the viscosity of the paint so that it is more easily applied. Varnishes are similar except that they contain a resin in place of the pigments. Linoleum contains a mixture of a drying oil and ground cork which has been allowed to harden by exposure to the air.

As has been stated, the melting point of an oil is determined in part by its unsaturation. Hydrogenation, then, is capable of converting an oil to a fat. The products are sold as shortening for baking and as margarine. The hydrogenation is accomplished by use of elemental hydrogen and a nickel catalyst. Depending on the consistency desired, the reaction may be stopped at any point. It is thus possible to make a harder product in the summer than in winter. The hydrogenation process, because of the change in physical properties accompanying it, is sometimes called the "hardening of oils."

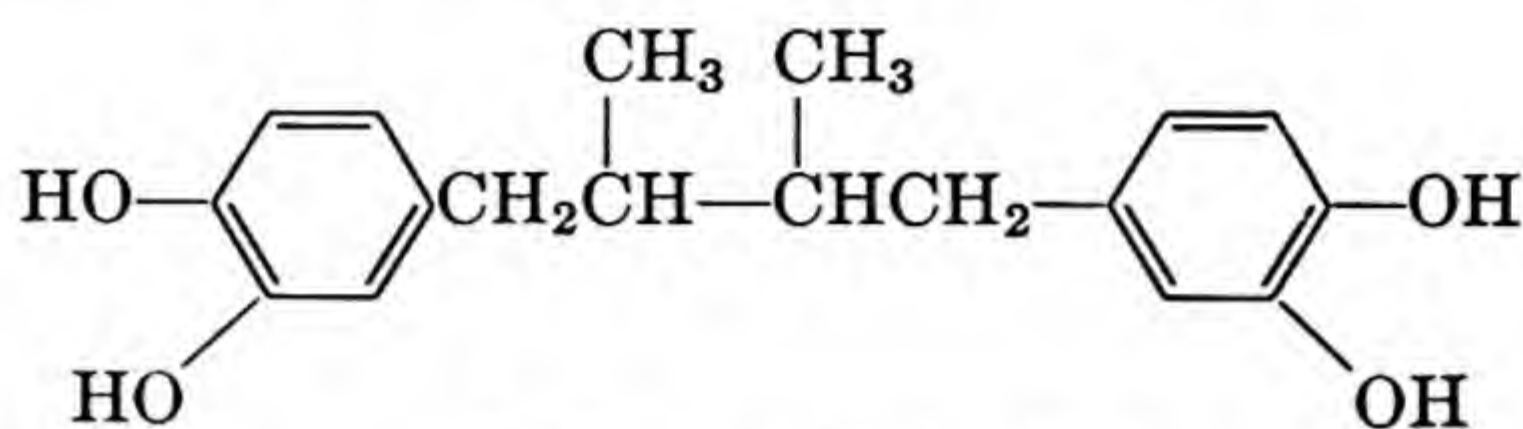
A difficulty with edible oils and fats has been the development of rancidity. The cause is oxidative cleavage of the unsaturated linkages in the fat or oil, and the outward manifestations constitute a darkening in color and an offensive odor. The latter is caused by the production of fatty acids of moderate molecular weight, such as pelargonic acid, which can be formed from oleic acid.



Substances which inhibit oxidation are now incorporated into edible fats. The use of 0.01% nordihydroguaiaretic acid, for example, al-



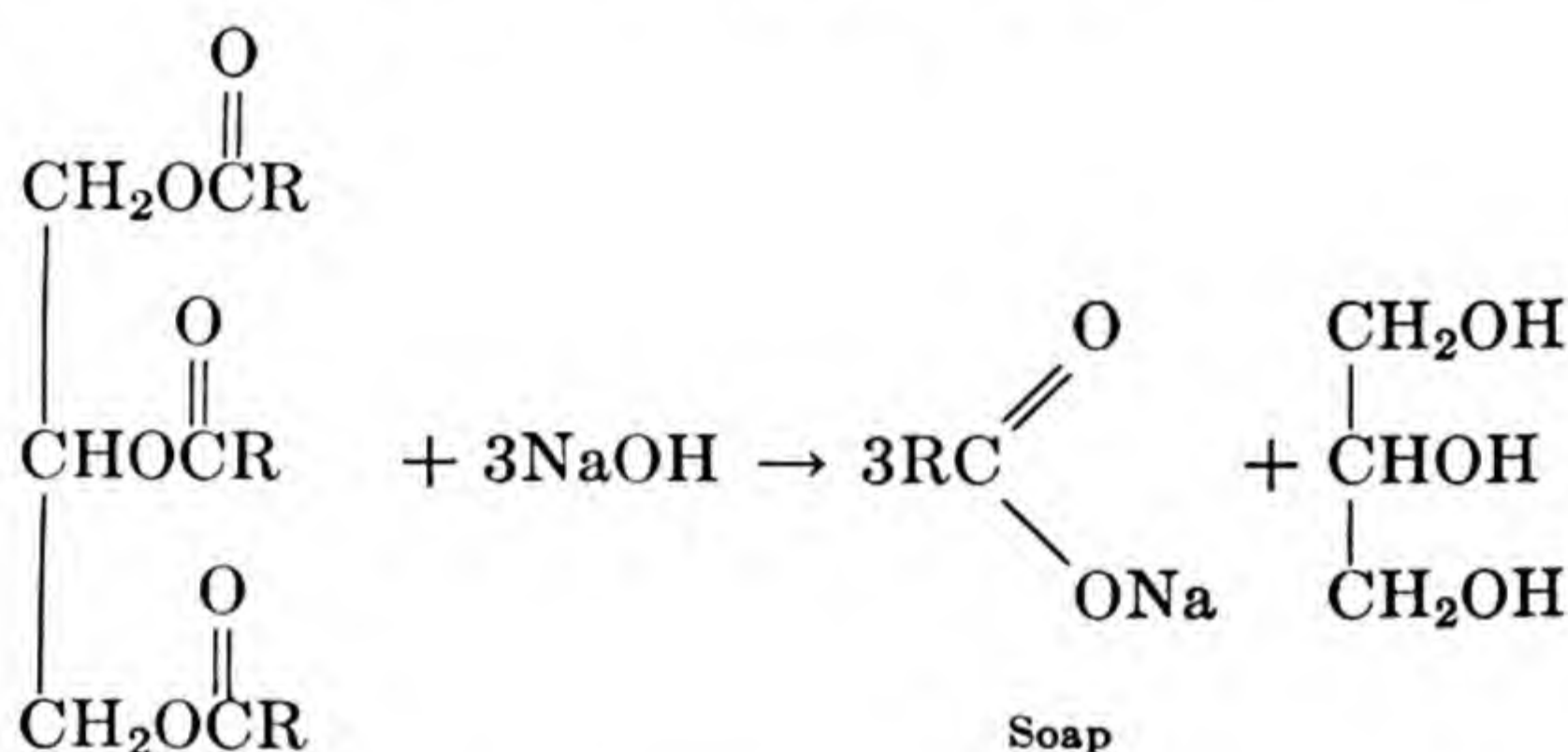
lows storage of lard at room temperature for over a year without the development of rancidity.



Nordihydroguaiaretic acid

## ► SOAPS

Soaps are defined as the metallic salts of long-chain fatty acids. This definition includes some substances—the salts of elements other than Group I of the periodic table—that have no cleaning power in water. Those used for cleaning are the sodium and potassium salts; they are made by the saponification of fats.

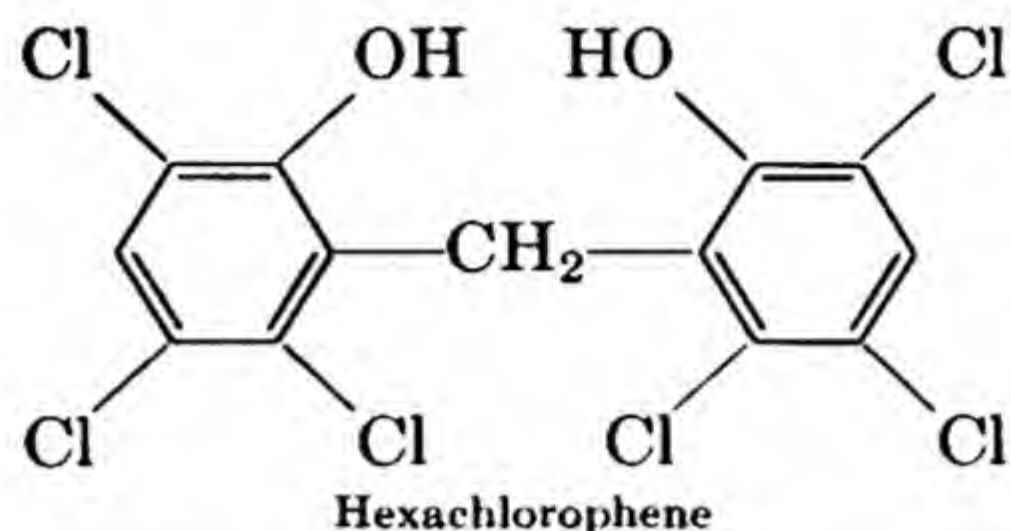


Since the fats themselves are complex mixtures, it follows that commercial soaps are complex also, and their composition varies with the type of fat used in their manufacture. Glycerol is an important by-product of the soap industry.

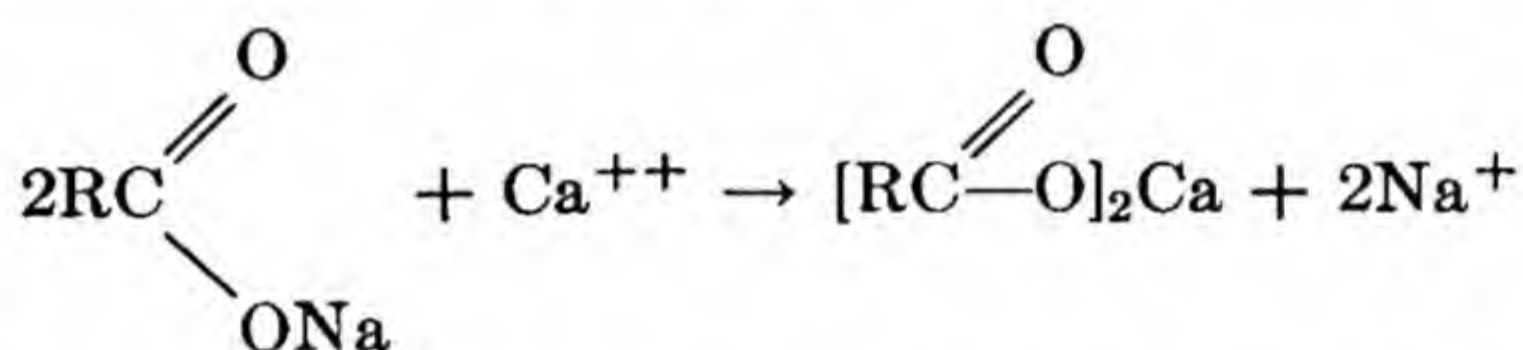
Aqueous soap solutions have the power of emulsifying oil, grease, and dirt and so aid in the removal of these substances. The sodium and potassium soaps differ considerably in physical properties: the sodium soaps are harder than the potassium. In commercial soaps certain substances other than the soaps themselves are present, depending upon the use to which the soap is to be put. All contain water, and nearly all, some fragrant substance. Some laundry soaps contain an optical bleach, a substance which absorbs ultraviolet radiation and emits blue light. The blue light “neutralizes” the yellow color which fabrics take on when they have been washed repeatedly. Floating soaps are made by beating air into the soap before it is pressed into cakes. Scouring soaps contain abrasives, such as silica



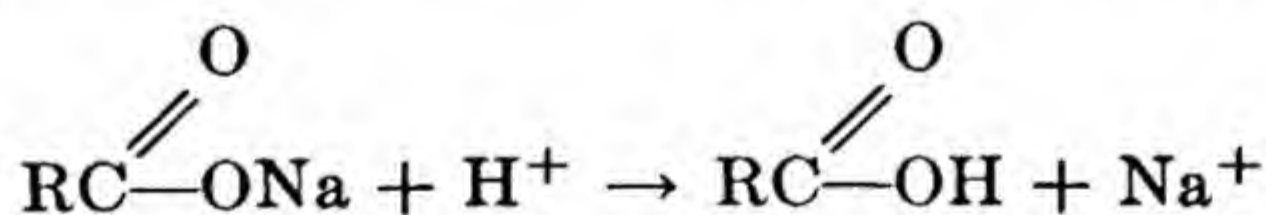
or pumice, and sodium carbonate or trisodium phosphate. The sap of certain trees is a source of rosin which contains complex organic acids, the salts of which have detergent properties and are introduced into laundry soaps. Shaving soaps contain rosin to help in the production of a good lather and glycerol and gum to prevent rapid drying. Some soaps contain germicides, usually phenols, such as phenol itself (p. 210), the cresols (p. 211), or "hexachlorophene."



Under certain conditions soaps do not function well as cleaning agents. Hard water contains the ions of calcium, magnesium, and iron, which react with the soap to produce insoluble salts.



These soaps appear as a scum which interferes with the cleaning process. In addition, considerably larger amounts of soap must be used in hard water than in soft water, since, in effect, the soap functions at first as a softener. Soaps do not function well in acid solutions because the fatty acid mixture precipitates. This situation is not often encountered in the home, but it does occur in industry.



Synthetic detergents have now replaced soaps to a considerable extent. They are discussed in the following section.

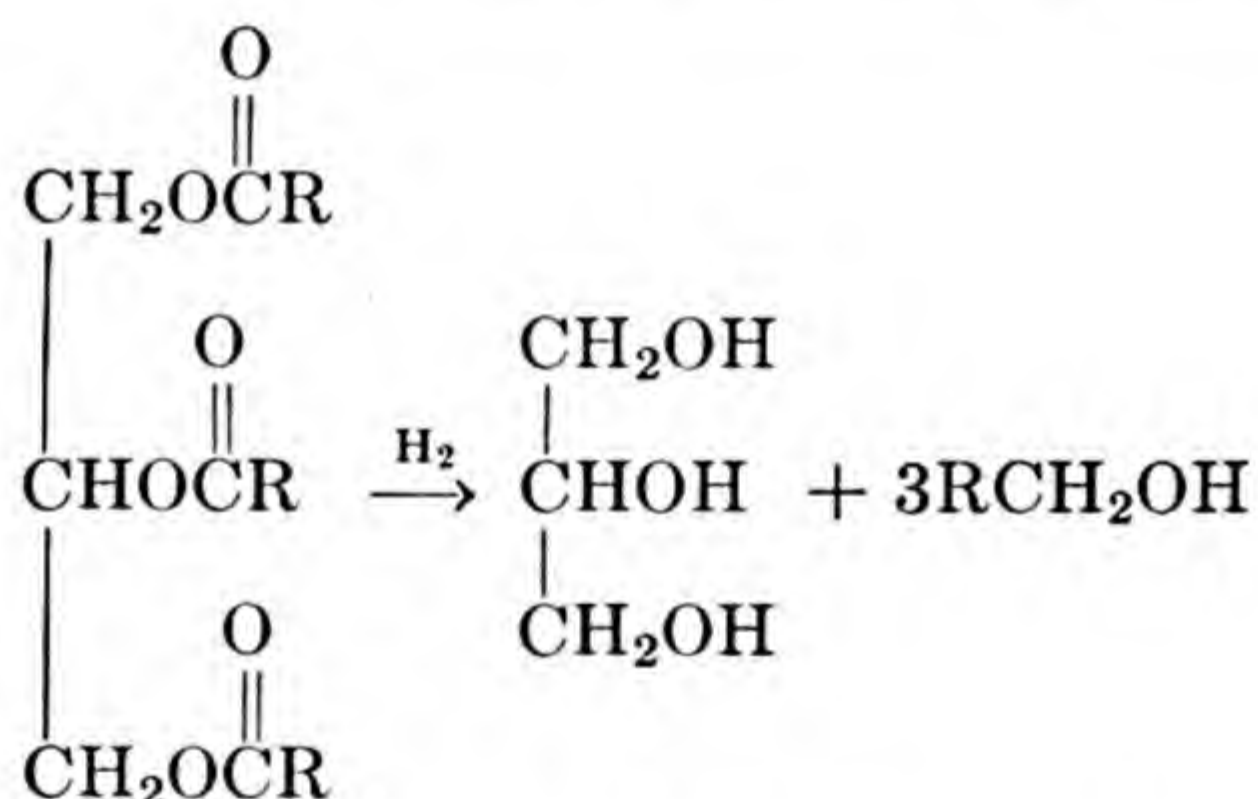
In addition to their employment as cleaning agents, soaps are used in other ways. Most greases consist of a lubricating oil and a soap: calcium, barium, and lead soaps as well as others are used in this application. Zinc stearate is employed in cosmetic powders, as a lubricant in molds, and as a waterproofing agent. Naphthenic acids, which are obtained from certain types of petroleum, react with bases to give salts much like the ordinary types of soap. Copper naphthenates are used in wood preservation and in antifouling paints.



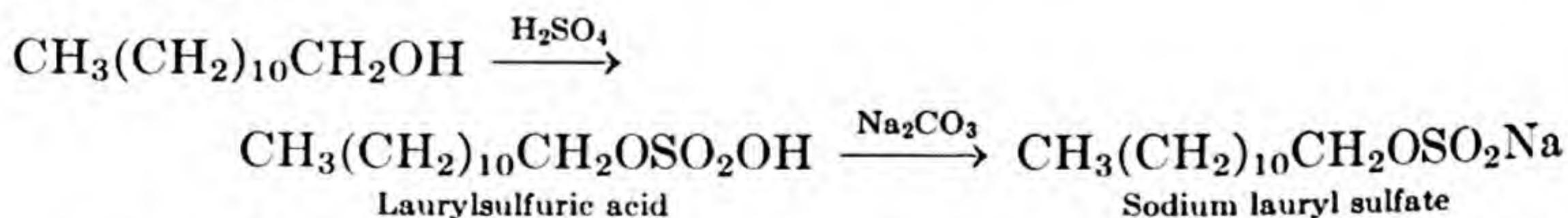
► **SYNTHETIC DETERGENTS**

The disadvantages of soaps have given impetus to the synthetic detergent industry. The use of synthetic detergents has been steadily rising and the sales volume surpasses that of soaps in the United States. The advantages of synthetic detergents are that they do not give precipitates in hard water and many of them are better emulsifiers than soaps. Their disadvantages are the higher costs involved and the difficulty with which they can be made into bars. The synthetic detergents have caused serious problems in sewage disposal plants. It has been found that settling of the sludge is much slower when synthetic detergents are present, and therefore the capacity of the disposal plants is lower.

Many synthetic detergents are structurally similar to soaps in that they are salts in which the negatively charged portion is a large organic fragment tending toward oil-solubility and the positively charged portion is a metallic ion tending toward water-solubility. An example of this type is the mixture of sodium alkylsulfates for which the starting material is coconut oil. The oil is treated with hydrogen and a copper-chromium oxide catalyst under high pressure and temperature.

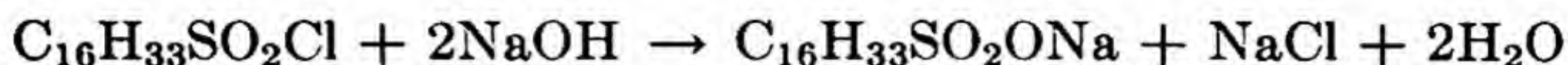
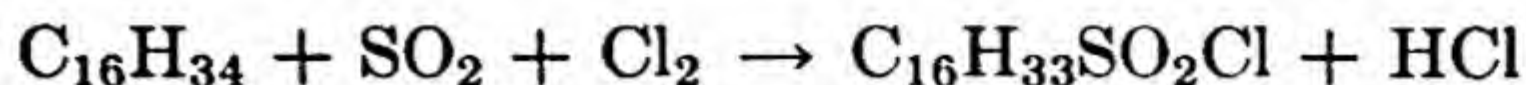


The mixture of alcohols produced, for the most part lauryl alcohol,  $\text{CH}_3(\text{CH}_2)_{10}\text{CH}_2\text{OH}$ , is treated with sulfuric acid to give an alkylsulfuric acid and then with sodium carbonate to give the salt, which is the detergent.

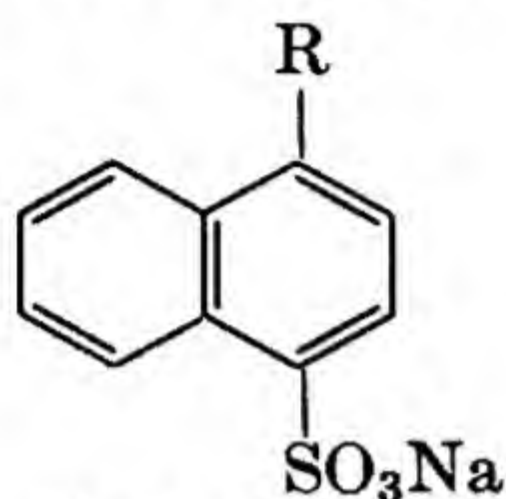


The alkylsulfonates are made from a high-boiling petroleum fraction by the following reaction in which hexadecane has been used as the example.

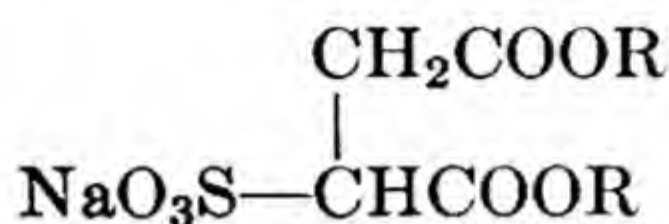




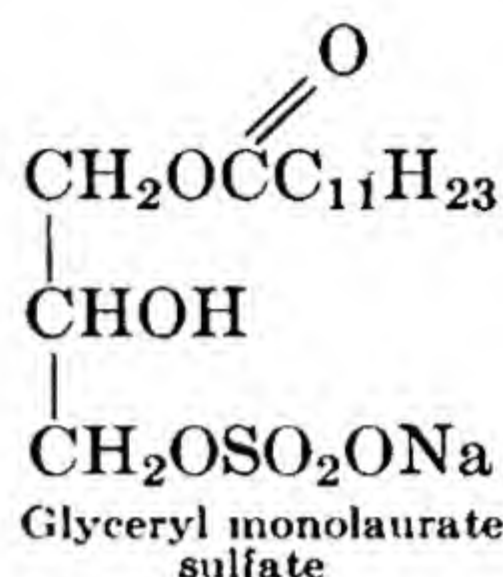
Other examples of synthetic detergents of this general type, in which R is a large group, are the following:



Alkyl aryl sulfonate

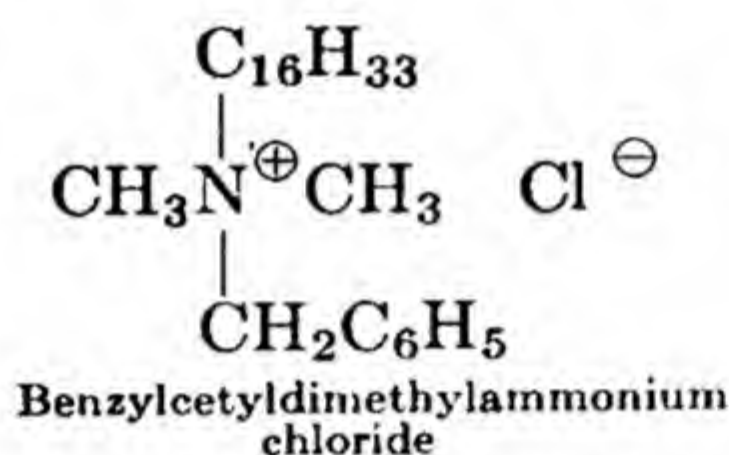


Sulfosuccinate



Glyceryl monolaurate sulfate

In the invert soaps the organic part of the molecule is positively charged. They are quaternary ammonium salts,  $\text{R}_4\text{N}^+\text{Cl}^-$  (Chapter 14), and are more bactericidal than soaps or other synthetic detergents. Some of them have been used in mouthwashes. Examples of invert soaps are given below.

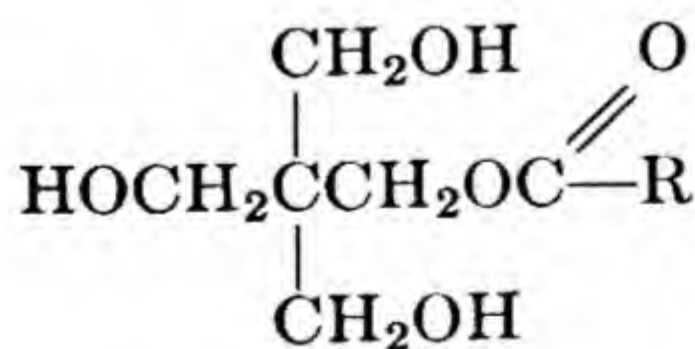


Benzylcetyldimethylammonium chloride

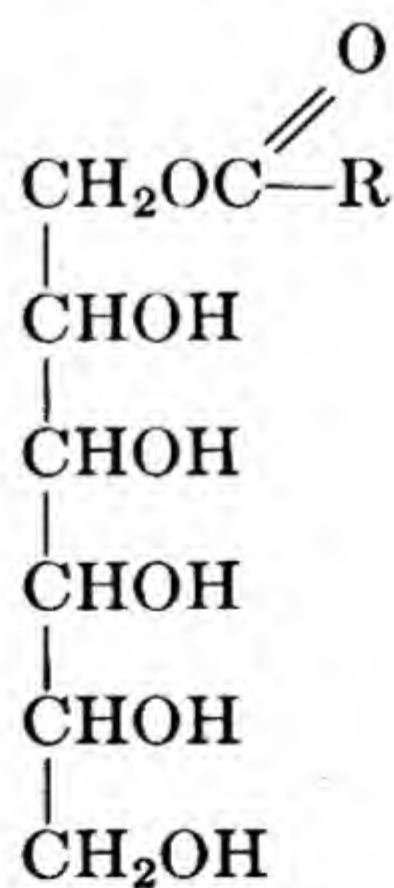


Cetylpyridinium chloride

A third type of synthetic detergent is nonionic. The water-solubilizing portion of the molecule has several hydroxyl groups; the oil-solubilizing portion is a long hydrocarbonlike chain. They are for the most part esters, and though the nonionic detergents are efficient they cause very little foaming in contrast to other synthetic detergents and soaps. Two types of nonionic detergents are shown below.



Pentaerythritol ester

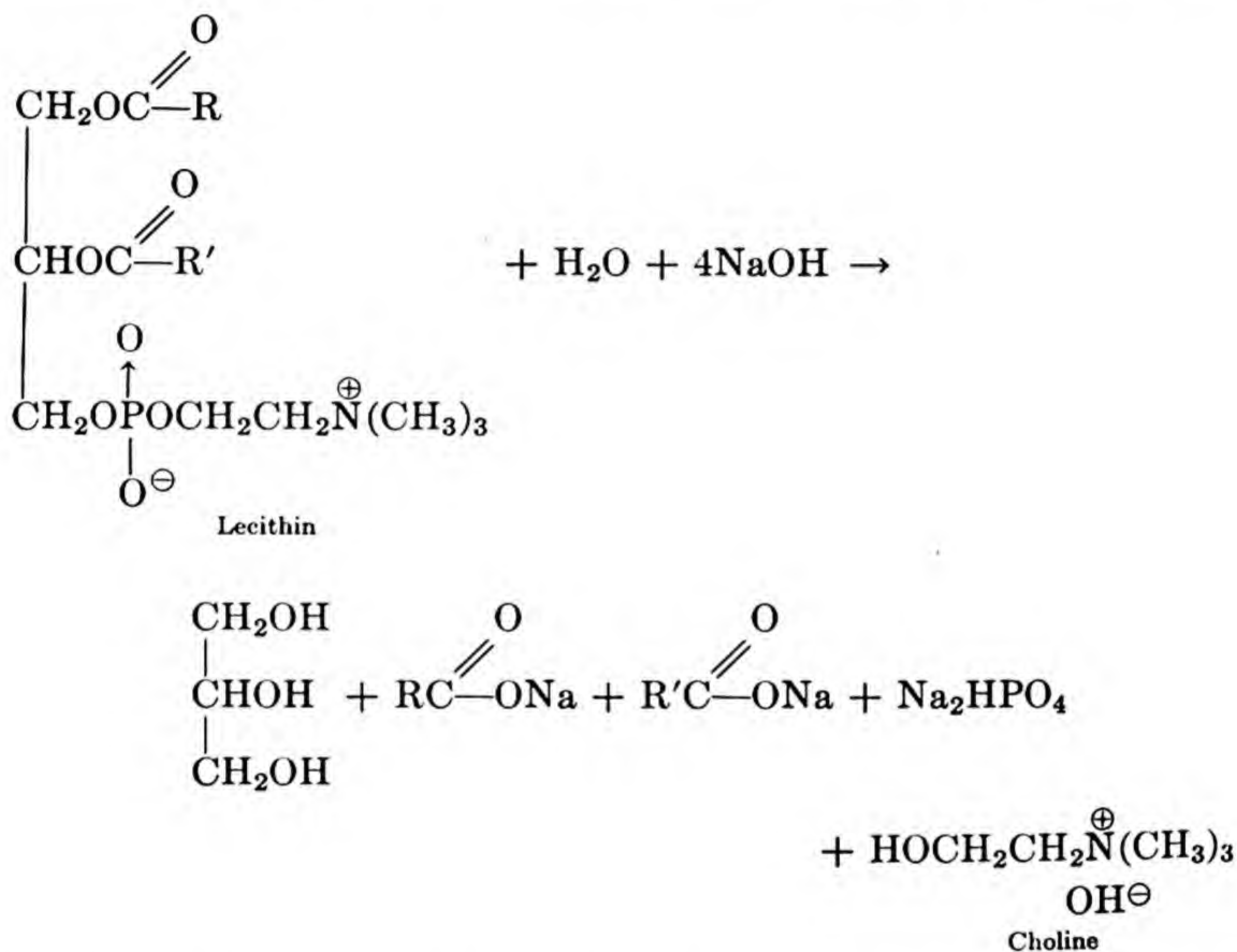


Sorbitol ester



► **PHOSPHOLIPIDS**

The phospholipids (also called phosphatides) are substances which upon hydrolysis yield glycerol, fatty acids, phosphoric acid, and a basic nitrogen compound. Lecithins, the most abundant type of phospholipid, give choline on hydrolysis. The various lecithins differ from each other in the identity of the R and R' groups and in the

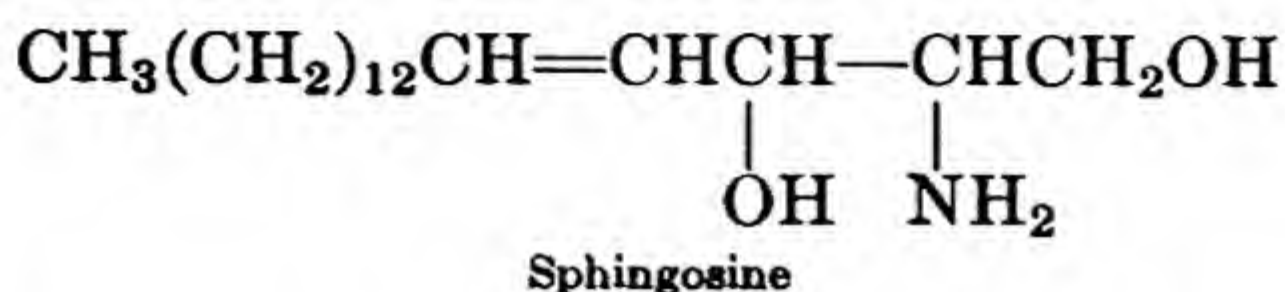


location of the phosphoric acid-choline residue which may be attached at the middle carbon atom of the glycerol. The lecithins belong to a class of compounds known as inner salts, or zwitterions, in which both the positive and negative charges are in the same molecule. Choline may be regarded as a substituted ammonium hydroxide; the four hydrogen atoms of the ammonium ion have been replaced by alkyl groups.

The cephalins constitute another class of phosphatides. Instead of choline, they give ethanolamine,  $\text{HOCH}_2\text{CH}_2\text{NH}_2$ , upon hydrolysis.

The sphingolipids have a somewhat different type of structure than the cephalins and lecithins. Sphingomyelin, an example, yields choline, phosphoric acid, a fatty acid, and sphingosine upon hydrolysis.



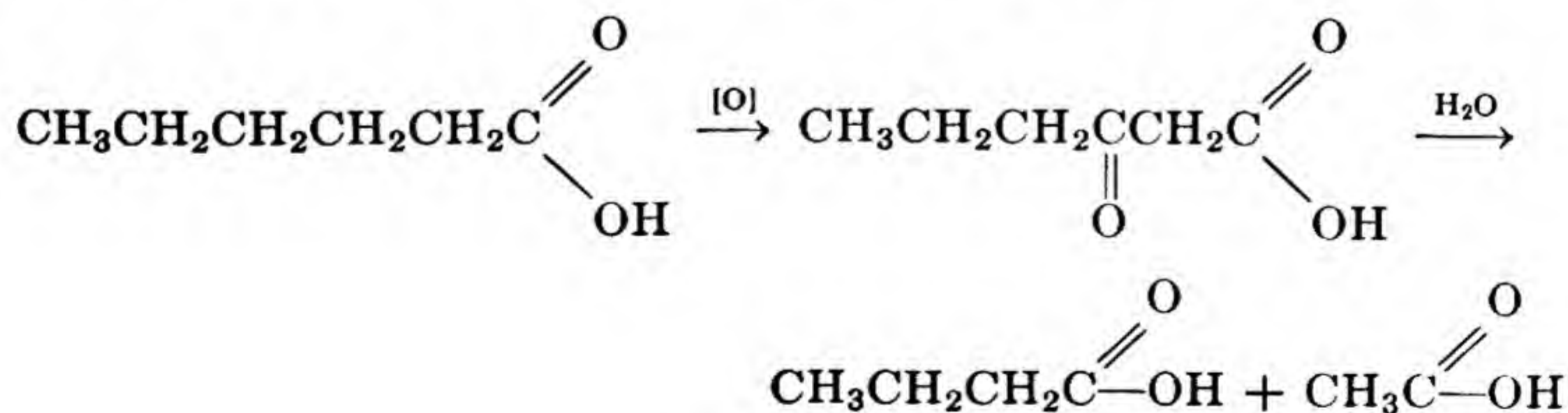


Phosphatides occur widely in plant and animal tissue and appear to be present in every cell. They are particularly abundant in active tissue, such as the brain, liver, heart, kidneys, and nerves.

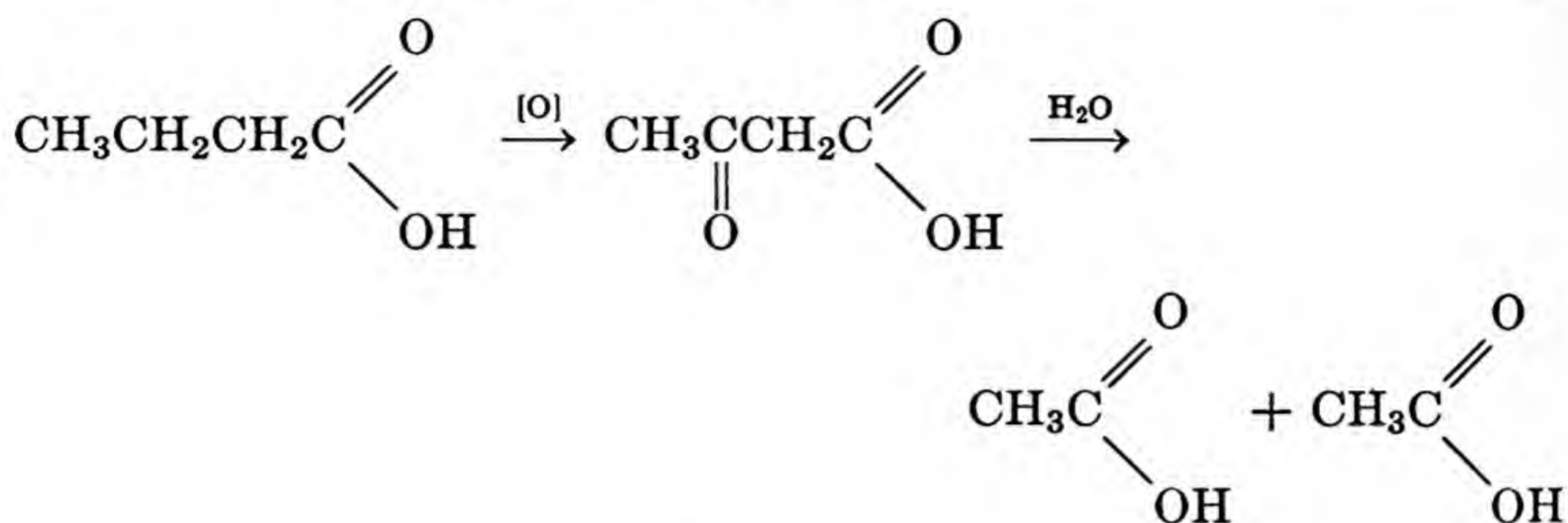
## ► DIGESTION AND METABOLISM OF FATS

No digestion of fats occurs in the mouth. Though the stomach juices appear to be capable of hydrolyzing fats to some extent, nearly all this process occurs in the small intestine, the contents of which are slightly alkaline and therefore more favorable to ester hydrolysis. Enzymes capable of hydrolyzing fats or oils are called lipases; two of them appear to be important in the human. One (steapsin) is produced by the pancreas and secreted into the small intestine, and the other is produced in the walls of the small intestine itself. With the aid of the bile salts, which are produced by the liver and stored in the gall bladder, these enzymes catalyze the hydrolysis of the glycerides to glycerol and mixtures of fatty acids. The bile salts are soaplike materials that perform the important function of emulsifying the fats, which are not soluble in the intestinal juices. The hydrolysis products are absorbed by the wall of the intestine and are recombined to form glycerides, though not necessarily the same as those originally ingested. The fats are transported in the body by the blood and the lymph.

Fats are oxidized by the body to carbon dioxide and water for the production of energy. The mechanism which is accepted for this transformation is known as Knoop's  $\beta$ -oxidation for its originator. In essence, the theory states that oxidation occurs in two-carbon steps and produces acetic acid or some related compound. With caproic acid as the example, the oxidation can be represented as follows:







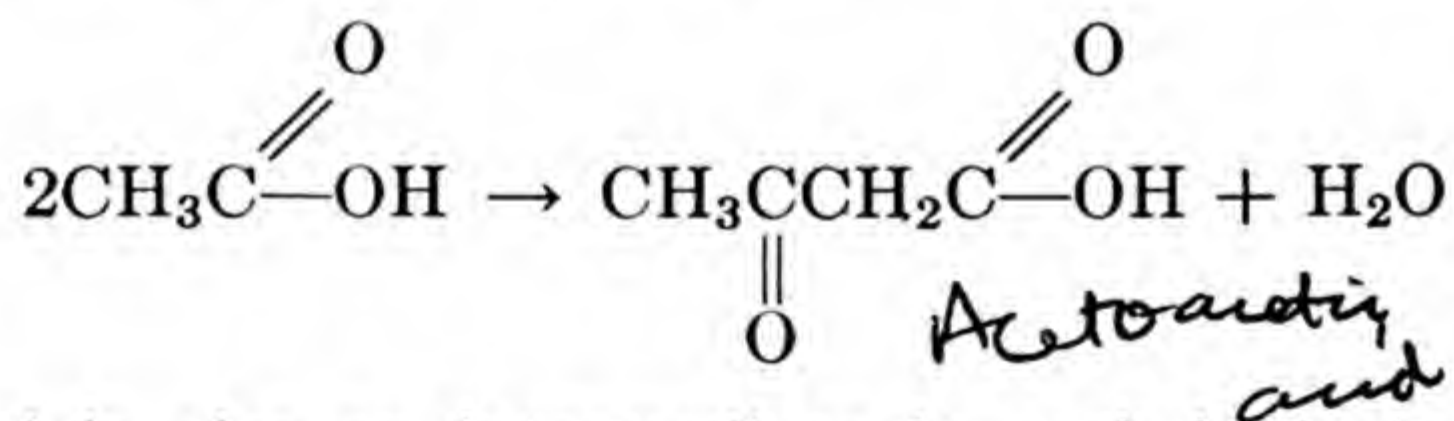
The scheme would apply as well to stearic acid, from which palmitic acid would be produced, then myristic acid, and so on. The chain would be successively shortened by two carbon atoms.

Support for the  $\beta$ -oxidation scheme was found by Knoop in certain feeding experiments. Additional evidence for the theory is that dia-

betics excrete acetoacetic acid,  $\text{CH}_3\text{CCH}_2\text{C}$   $\begin{array}{c} \text{O} \\ \parallel \\ \text{O} \end{array}$   $\begin{array}{c} \text{O} \\ \parallel \\ \text{OH} \end{array}$ , when fats are in-

gested. Acetone and  $\beta$ -hydroxybutyric acid,  $\text{CH}_3\text{CHCH}_2\text{C}$   $\begin{array}{c} \text{O} \\ \parallel \\ \text{OH} \end{array}$   $\begin{array}{c} \text{O} \\ \parallel \\ \text{OH} \end{array}$ , are

also produced, but these substances can easily come from acetoacetic acid. It was formerly thought that acetoacetic acid represented the final product of fatty acid metabolism in the diabetic. More recent evidence indicates, however, that this substance is produced by the condensation of two molecules of acetic acid.



Acetic acid is also an intermediate in carbohydrate metabolism. Its conversion to carbon dioxide and water is a very complex process.

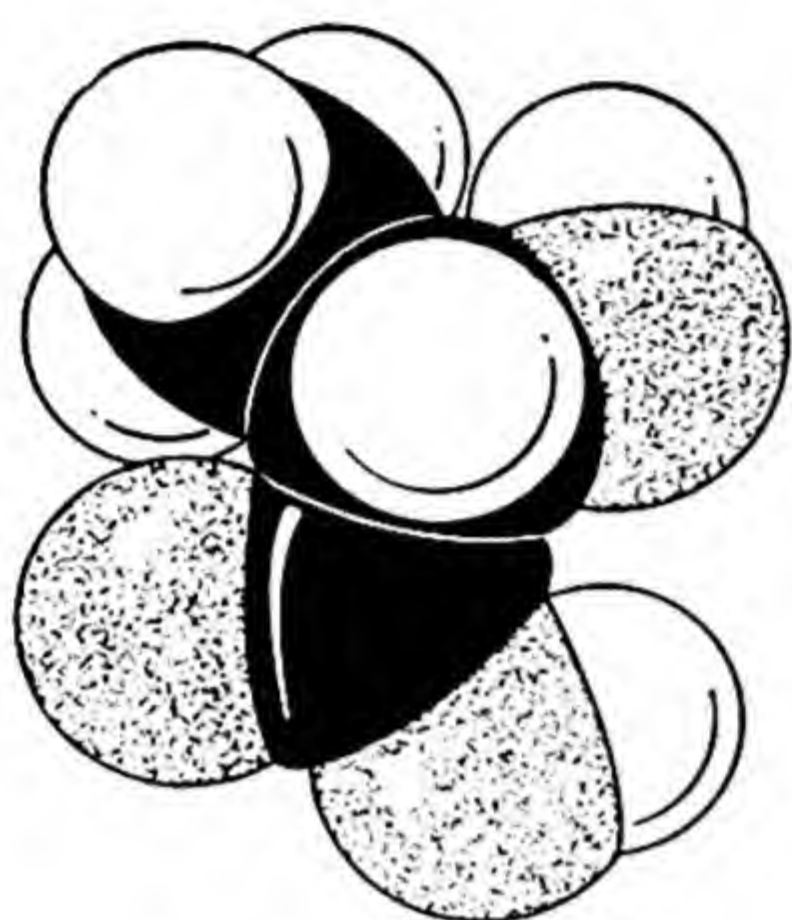
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► QUESTIONS

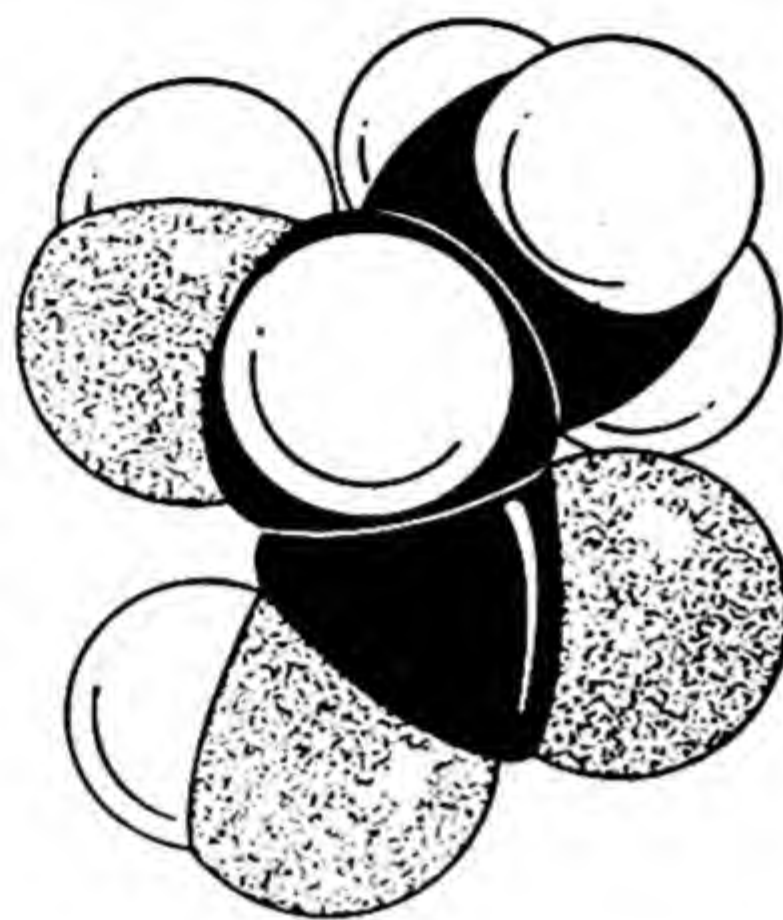
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1. Define or explain the meaning of the following terms: soap, glyceride, lipase, phosphatide, drying oil.
2. Oleic acid and elaidic acid are *cis-trans* isomers. Oleic acid has been shown to have the *cis* configuration. Write the configurational formulas for both acids. Linoleic acid has the *cis-cis* configuration. Write its formula.
3. Write the formula for a cephalin and show how it is hydrolyzed.
4. Suppose that a natural fat yields a mixture of stearic and palmitic acids on hydrolysis. Write the structural formulas for the glycerides that could be present in the original fat.





D-Lactic acid



L-Lactic acid

Though the two lactic acids have the same structural formula,  $\text{CH}_3\text{CHCOOH}$ , they differ in their configuration



about the central carbon atom. The models show that the molecules are nonsuperimposable mirror images. The physical and chemical properties of such mirror images are identical except for their rotation of the plane of polarized light. Though the amount of rotation is the same, the direction is opposite.

### ► POLARIZED LIGHT

In order to understand the phenomenon of optical isomerism, it is necessary to have some knowledge of plane polarized light. If we were able to view a single wave of light broadside, the appearance



Figure 1



Figure 2

would be somewhat like Figure 1. Viewed endwise, the beam would appear as in Figure 2. The light from most sources, however, has beams vibrating in many planes which are at various angles to each other, as in Figure 3 (much simplified). Certain materials, such as

tourmaline, a silicate mineral, have the ability to “filter out” all light vibrations except those in certain parallel planes. Such light is said to be plane polarized, and Figure 4 is an example of what might be the result of such filtering action, with the polarized light viewed endwise.

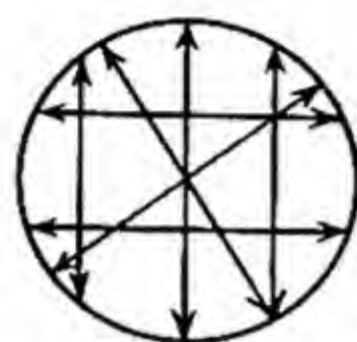


Figure 3

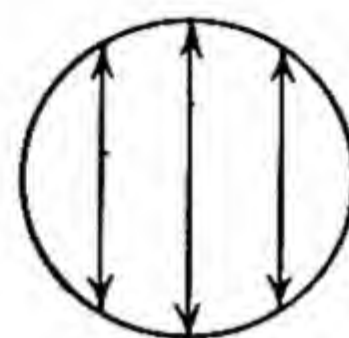


Figure 4

Interesting experiments can be performed with two tourmaline lenses. If they are placed in front of a light source with their axes parallel, as in Figure 5, the first lens will “polarize” the light. Such polarized light will pass through the second lens also. However, if the second lens is rotated so that its axis is perpendicular to that of the first, the polarized light produced by the first lens will not pass the second, and the latter will appear opaque (Figure 6).



Figure 5



Figure 6

## ► OPTICAL ACTIVITY

Optical activity can best be described by reference to the instrument used to measure it, the polarimeter (Figure 7). This instru-

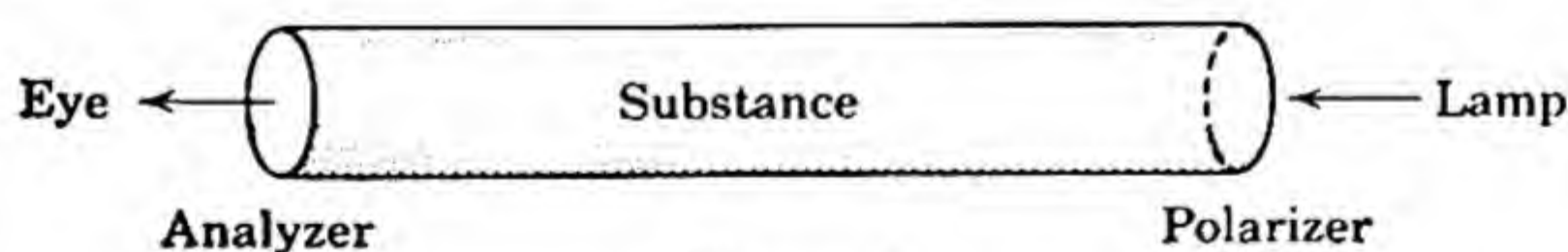


Figure 7

ment consists essentially of a long tube containing two tourmaline lenses near its ends. One of these, the polarizer, is fixed. The other, the analyzer, can be rotated, and the amount of rotation can be measured. With the analyzer set at zero, light passing through the polarizer also passes through the analyzer, as in Figure 5. If a sample of certain substances is placed between the polarizer and



analyzer, it is found that the analyzer must be rotated in order to allow the light to pass through. The explanation is that the substance has rotated the plane of polarized light. Thus light leaving the polarizer might be represented as in Figure 8, that leaving the substance as in Figure 9. It is necessary, therefore, to rotate the analyzer

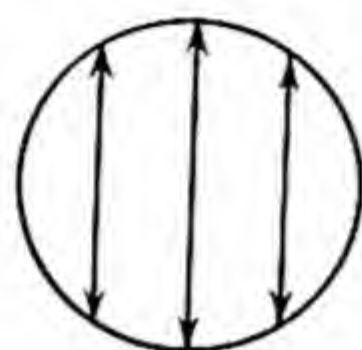


Figure 8

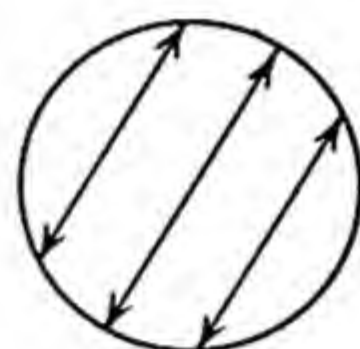


Figure 9

to compensate for the rotation of the plane of vibration of the light by the substance. A substance which has this ability is said to be *optically active*. Many such materials occur naturally; sugars, proteins, and alkaloids are examples.

The magnitude of the optical rotation of a substance varies with a number of factors such as temperature, concentration, and the wavelength of the light used. In order to make observed rotations comparable, it is desirable to convert them into specific rotations. For solutions the formula employed is  $[\alpha]_{\lambda}^t = \frac{100\alpha}{lc}$ , in which  $[\alpha]_{\lambda}^t$  is the specific rotation at some temperature  $t$  and wavelength  $\lambda$ ,  $\alpha$  is the observed rotation,  $l$ , the length of the tube in decimeters and  $c$ , the concentration in grams per 100 ml of solution. Usually the solvent in which the measurements were taken is specified because it may also have an effect on rotation.

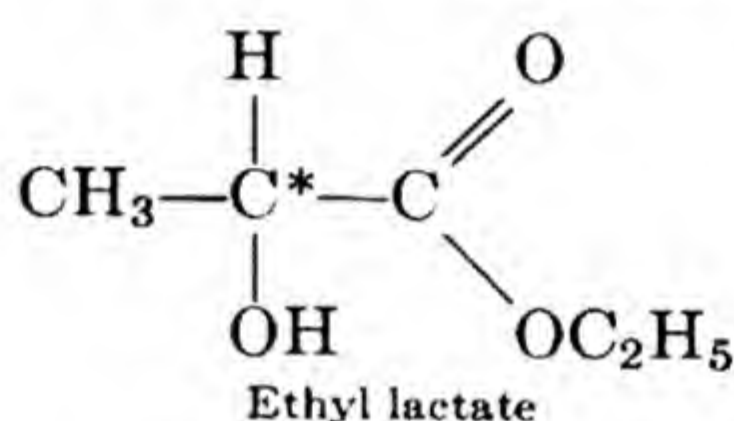
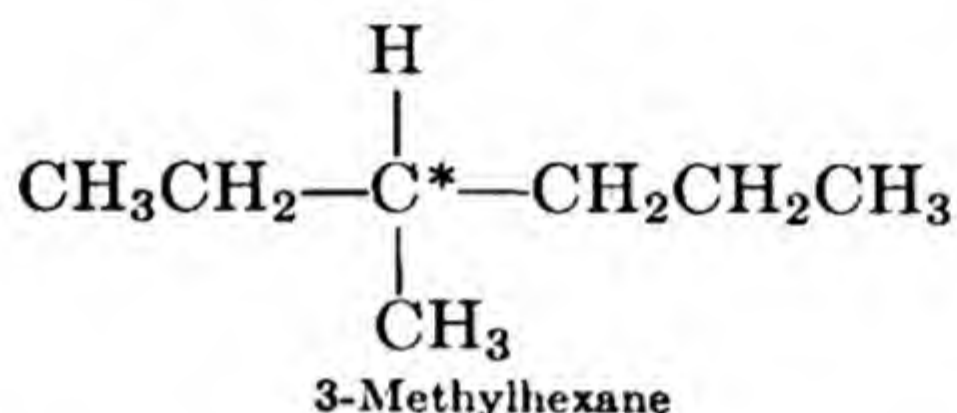
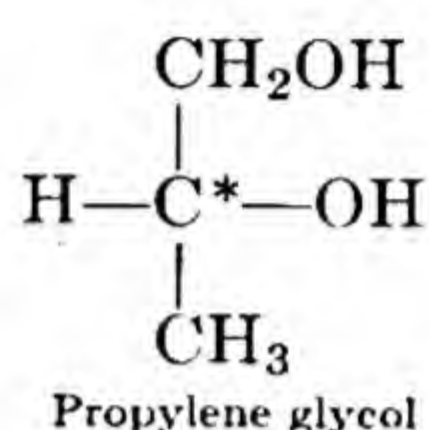
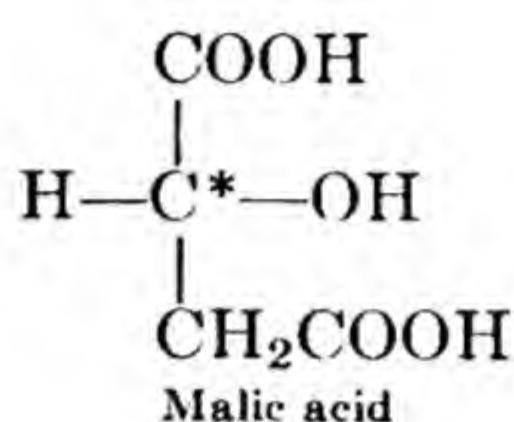
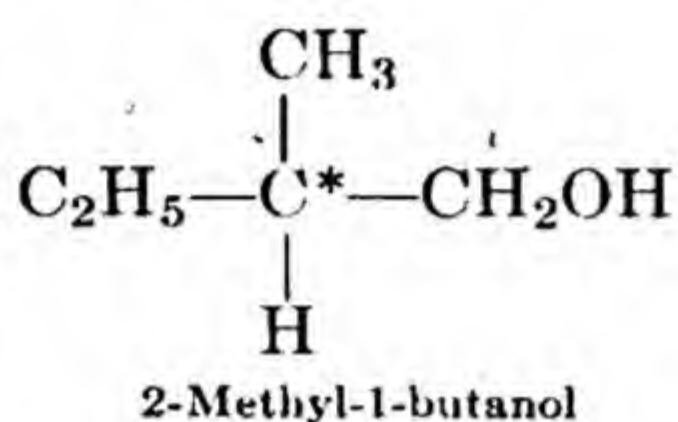
## ► OPTICAL ISOMERS

It is remarkable that there are isomers which have the same structural formulas and the same chemical and physical properties except for their effect on polarized light. For example, lactic acid from muscle tissue rotates the plane of polarized light in a clockwise direction, whereas lactic acid from the fermentation of certain sugars rotates the plane of polarized light to the same extent but counterclockwise. The first of these compounds is known as D-lactic acid and is said to be *dextrorotatory*. That from sugar fermentation is said to be *levorotatory* and is designated L-lactic acid. Synthetic lactic acid and that obtained from sour milk are identical and do not



rotate the plane of polarized light. This substance is called DL-lactic acid and consists of equal parts of the two optical isomers. Such substances are said to be *racemic*.

The phenomenon illustrated by lactic acid, mentioned in the preceding paragraph, is of frequent occurrence. Numerous instances are known in which isomers exist whose only chemical or physical differences consist in their effects on polarized light. The reason for the existence of such isomers may be arrived at by an examination of the structures of compounds that are optically active, examples of which are given here.



It can be seen that in each there is a carbon atom (indicated by an asterisk) which holds *four unlike atoms or groups*. Such an atom is said to be *asymmetric*. Whenever an asymmetric carbon atom is present in a molecule optical isomers can exist. The explanation of this phenomenon lies in the geometry of the tetrahedron. It will be recalled (Chapter 1) that the valences of a carbon atom are disposed in space so that the groups outline a tetrahedron. If a different atom or group (represented by *a*, *b*, *c*, and *d* in Figure 10) is attached to each of the four bonds of the carbon atom (at the center of the tetrahedron), two arrangements (or configurations) are possible:

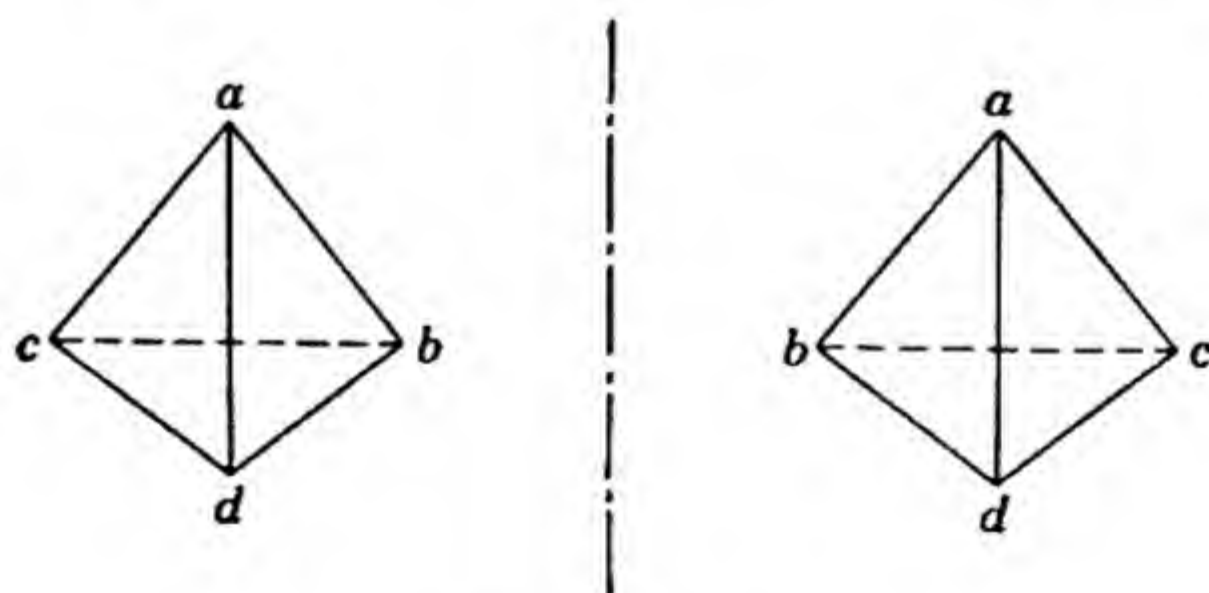


Figure 10

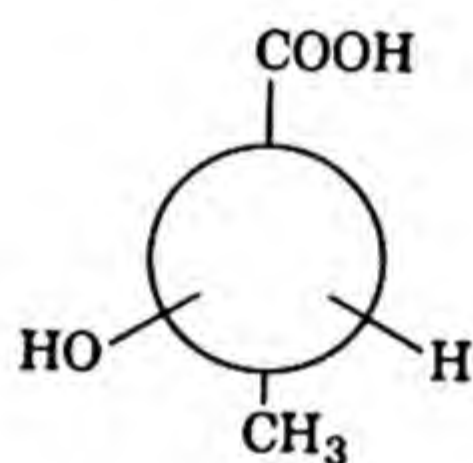


These cannot be superimposed; one is the nonidentical mirror image of the other. Neither of these configurational formulas has a plane of symmetry. That is, it is not possible to pass a plane through the tetrahedron in such a way as to cut it into identical halves.

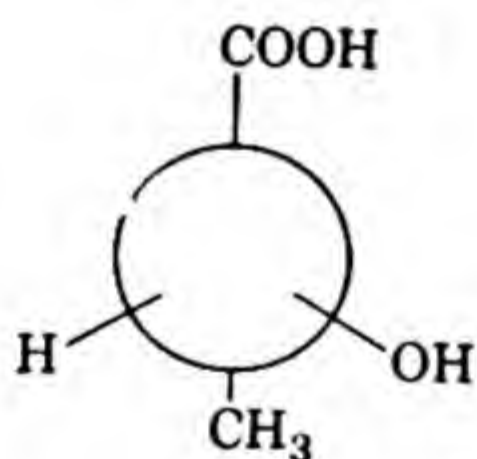
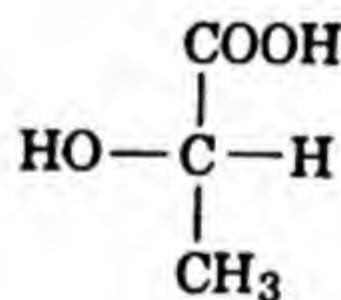
Thus the two compounds represented in Figure 10 have identical structures but different configurations. They are said to be *optical isomers*, and the phenomenon is spoken of as *optical isomerism*. Optical isomers that are mirror images, such as those in Figure 10, are termed *enantiomorphs*.

From the foregoing it follows that any structure which has an asymmetric carbon atom may exhibit optical isomerism; that is, two configurations, D- and L-, are possible.

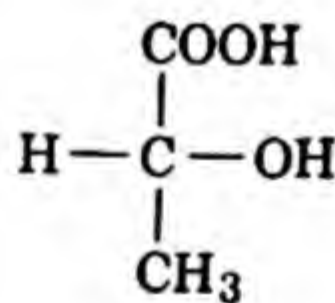
Various methods of representing asymmetric molecules, such as the tetrahedral representation in Figure 10, have been invented. One of the easiest to devise visualizes the central carbon atom as a sphere from which the valence bonds protrude. In the formulas for the two lactic acids, the bond to the carboxyl group is vertical and that to the methyl group is down and back. The two bonds to the hydroxyl group and to the hydrogen atom point up from the paper and outward.



L-Lactic acid



D-Lactic acid



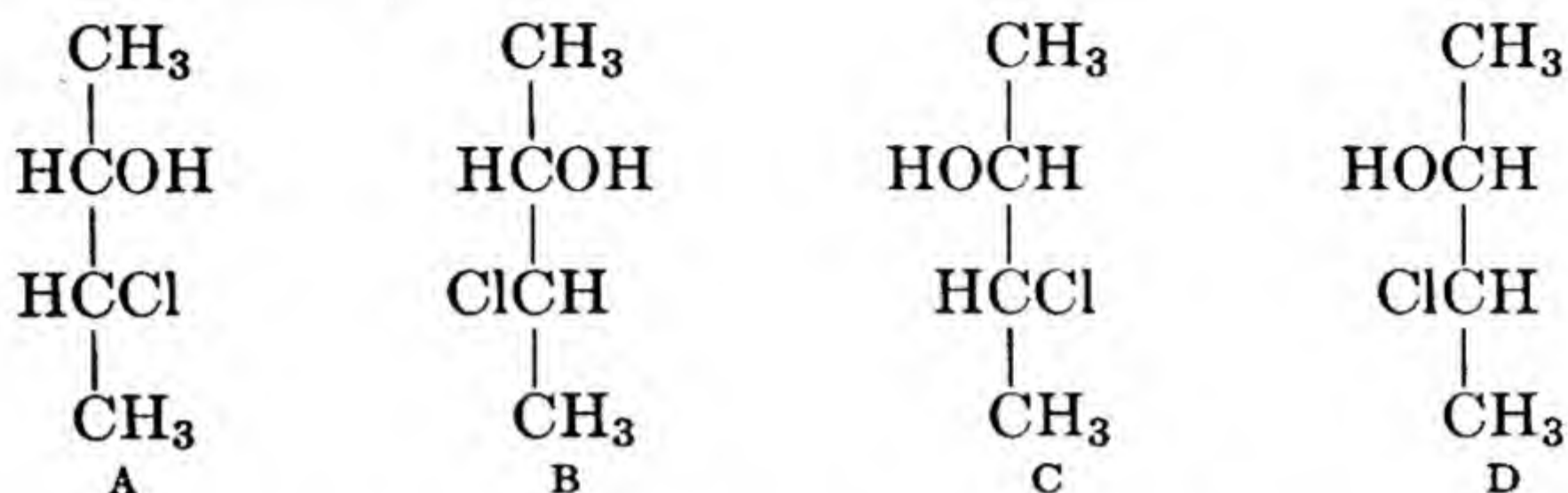
It is not always convenient to use spatial formulas to depict optical isomers, and planar representations are employed. They are in reality projections of the spatial models in which the three-dimensional formula is imagined to be above the plane of the paper. In the planar formulas the hydrogen atom and hydroxyl group should be visualized as protruding outward and toward the reader, as in the "sphere" formula.



Two dissimilar asymmetric carbon atoms can give rise to four optical isomers. For the molecule  $\text{CH}_3\text{CH}(\text{OH})\text{CH}(\text{Cl})\text{CH}_3$  the isomers could be



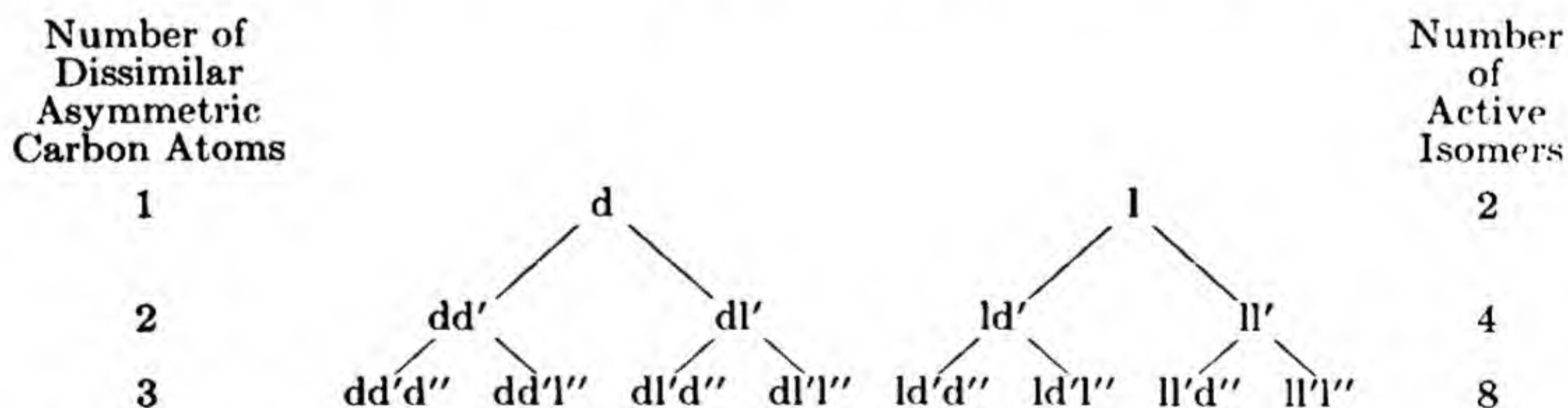
represented as follows:



It is instructive to consider the relationships of these configurations.

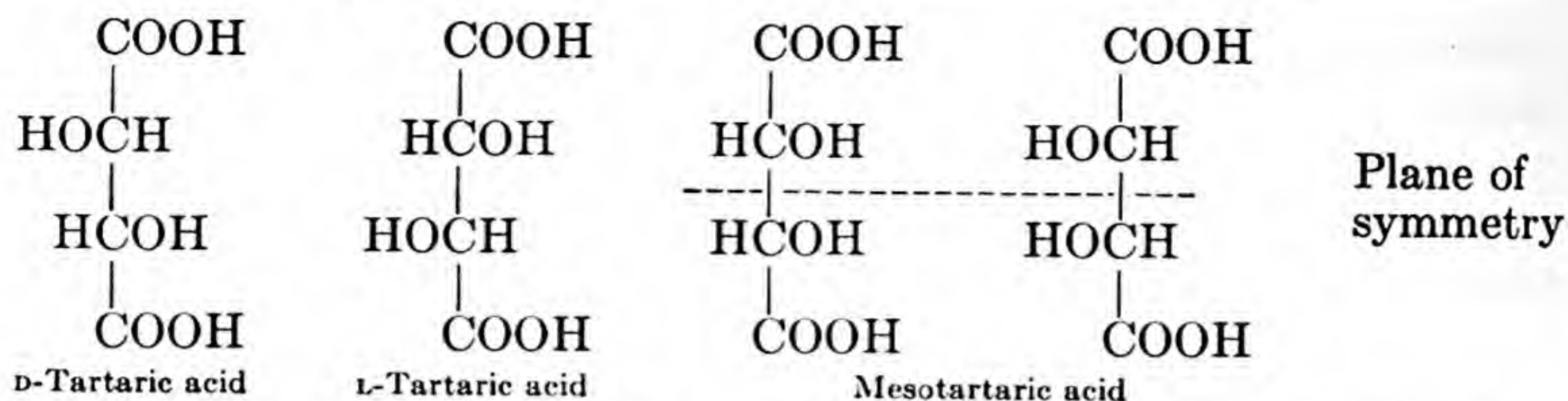
Examination reveals that A and D are enantiomorphs; one is the nonidentical mirror image of the other. Similarly, B and C constitute a pair of enantiomorphs. The chemical and physical properties of A and D are therefore identical except for their effect on polarized light. Similar considerations hold for B and C. On the other hand, the properties of A and B, though similar, would show definite observable differences. The term used for such optical isomers is *diastereoisomers*. They may be defined as *optical isomers which are not enantiomorphs*. Other pairs of diastereoisomers are A and C and C and D.

Three dissimilar asymmetric carbon atoms in a molecule give rise to eight configurations. This is evident in the following diagram. More generally, the number of optical isomers for a given structure is  $2^n$ , where  $n$  is the number of dissimilar asymmetric carbon atoms.

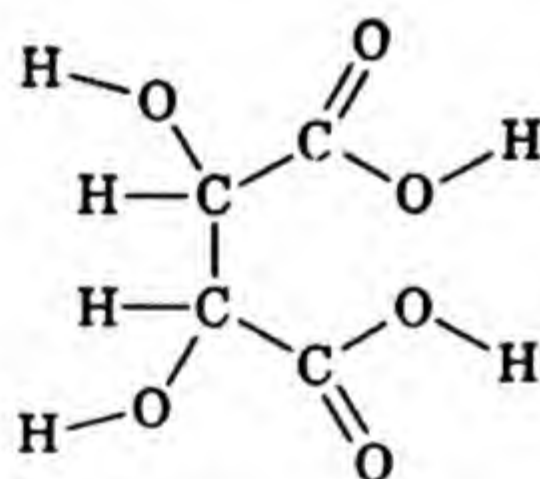
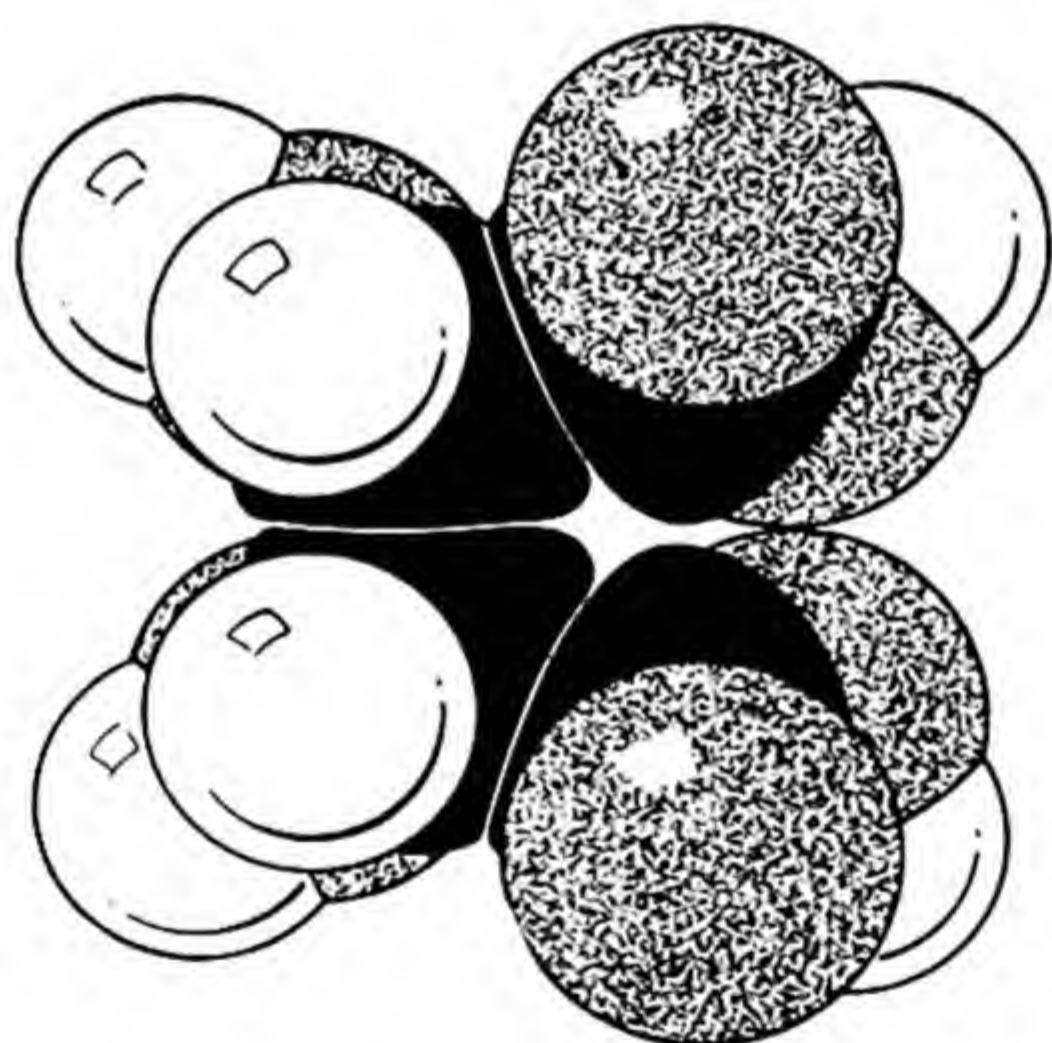


✓ **Meso Compounds.** Molecules such as tartaric acid exemplify a special case of optical isomerism. In this compound there are two asymmetric carbon atoms, but the groups attached to one carbon atom are the same as those attached to the other. As a result, only three optical isomers exist. The two formulas shown for mesotar-





taric acid are equivalent; if one of them is rotated  $180^\circ$  in the plane of the paper, it will be found that it coincides exactly with the other. Mesotartaric acid is inactive, since it has a plane of symmetry. One half of the molecule tends to rotate the plane of polarized light, but the other half, being its mirror image, compensates for this tendency, since it tends to rotate the plane of polarized light an equal amount but in the opposite direction. *Meso* compounds are thus "internally compensated," since the neutralization of activity occurs within a single molecule. In contrast, racemic (DL) mixtures are optically inactive because of external compensation. Any single molecule in a DL-mixture is optically active, but compensation is effected by another molecule having equal rotatory power but opposite in sign.



Mesotartaric acid

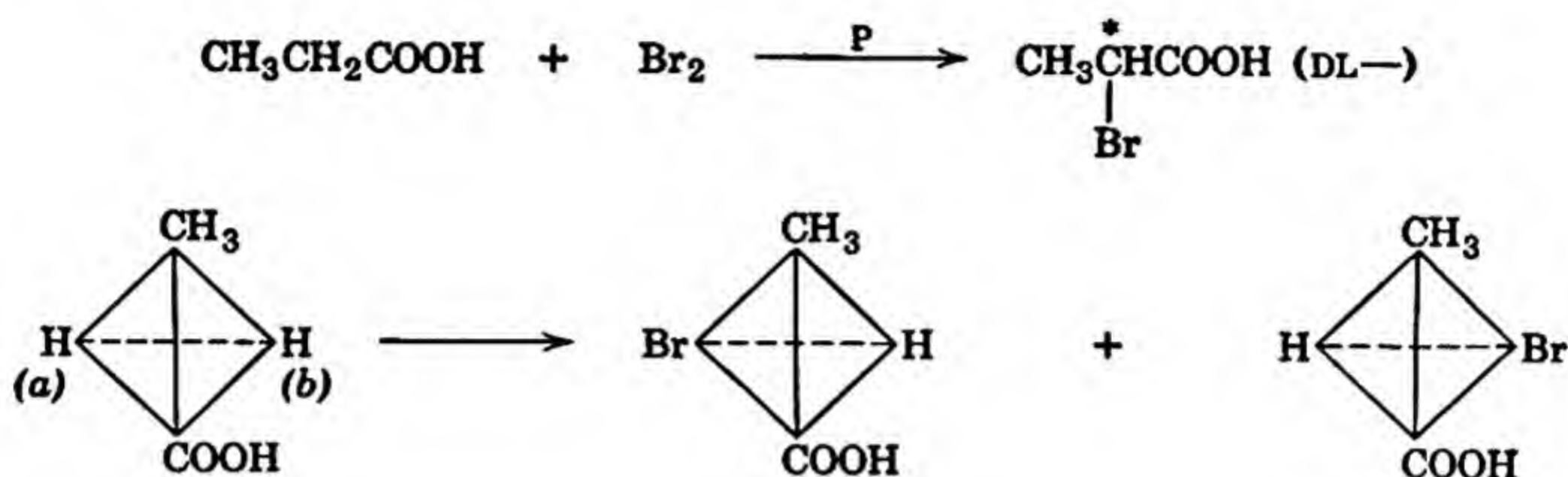
Meso compounds are a special kind of optical isomer. They possess a plane of symmetry and are therefore optically inactive.

## ▶ RESOLUTION

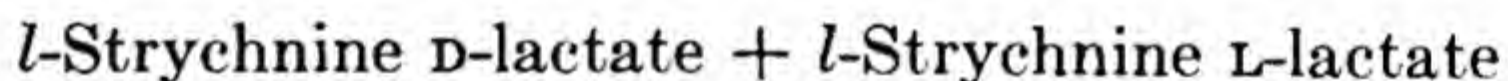
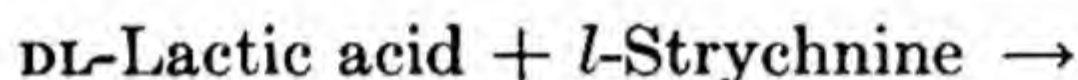
In the laboratory a reaction leading to the formation of an asymmetric molecule from optically inactive starting materials always yields a racemic mixture. The reason can readily be seen from an example. If propionic acid is brominated, DL- $\alpha$ -bromopropionic acid



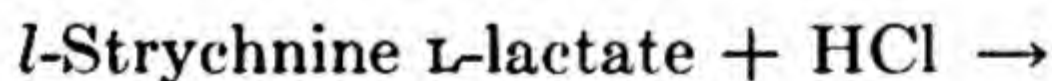
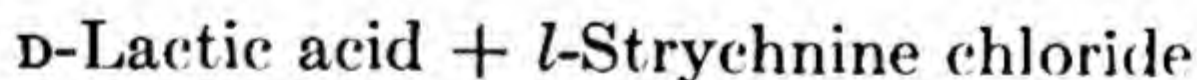
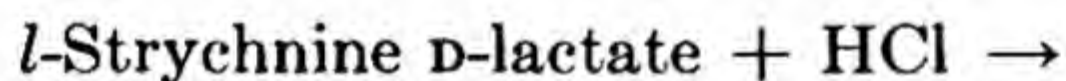
results. In the spatial formula for propionic acid the two hydrogen atoms at *a* and *b* can be seen to be equivalent. Replacement of one or the other is equally likely, and therefore it would be expected that the D- and L- bromo acids would be formed in equal amounts.



For biochemical experiments and for investigation of the mechanisms of organic reactions it is often necessary to use optically pure materials. The separation of the isomers in a DL-mixture is important. Any process for doing this is termed *resolution*. No general methods of resolution are known, but that having the greatest application is the method of diastereoisomers. It can be illustrated by the resolution of DL-lactic acid with *l*-strychnine, a naturally occurring basic substance. Two salts are formed in the reaction.



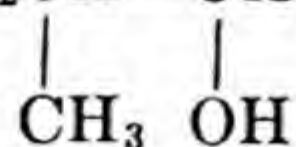
The two salts are diastereoisomers, and thus their properties differ. In this instance they can be separated by fractional crystallization. Treatment of the pure salts separately with hydrochloric acid regenerates the optically pure acids:





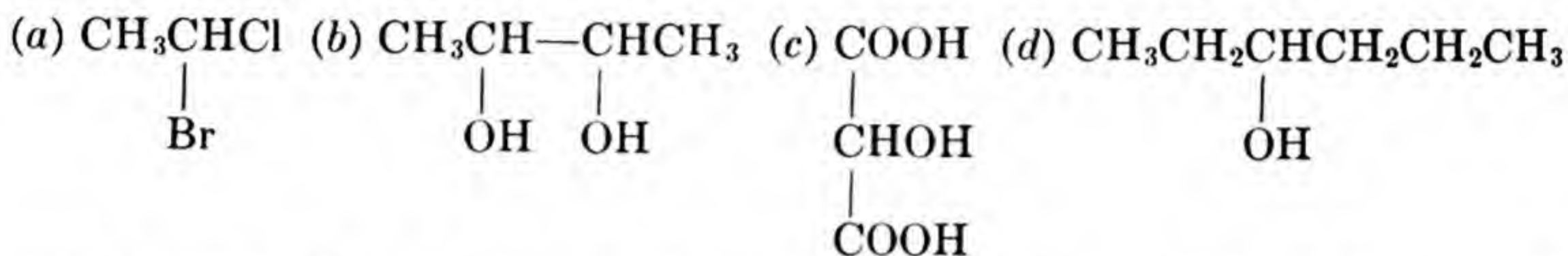
## ► QUESTIONS

1. Write configurational formulas for the four optical isomers represented by the structural formula  $\text{CH}_3\text{CH}_2\text{CH}-\text{CHCH}_3$ . Show which pairs of struc-

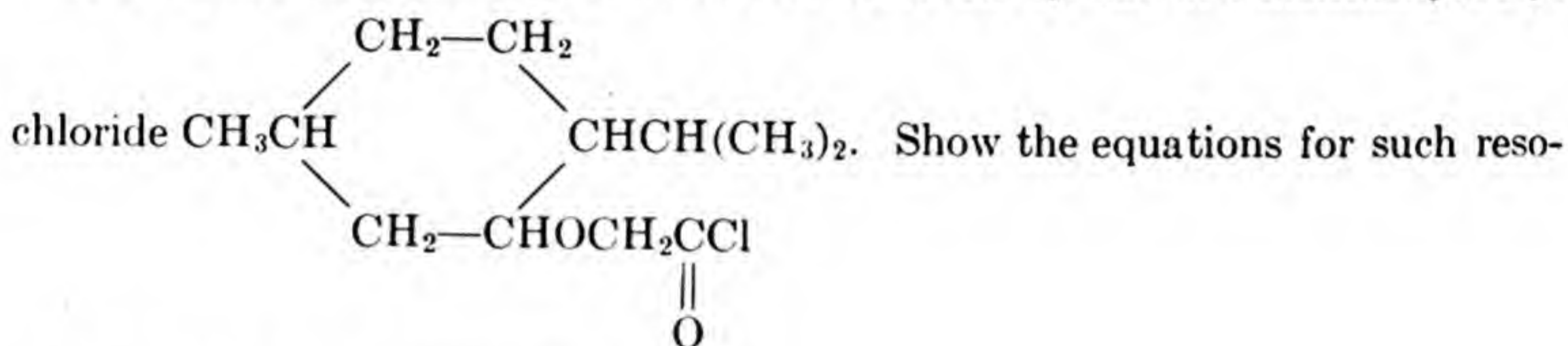


tures are enantiomorphous and which are diastereoisomeric.

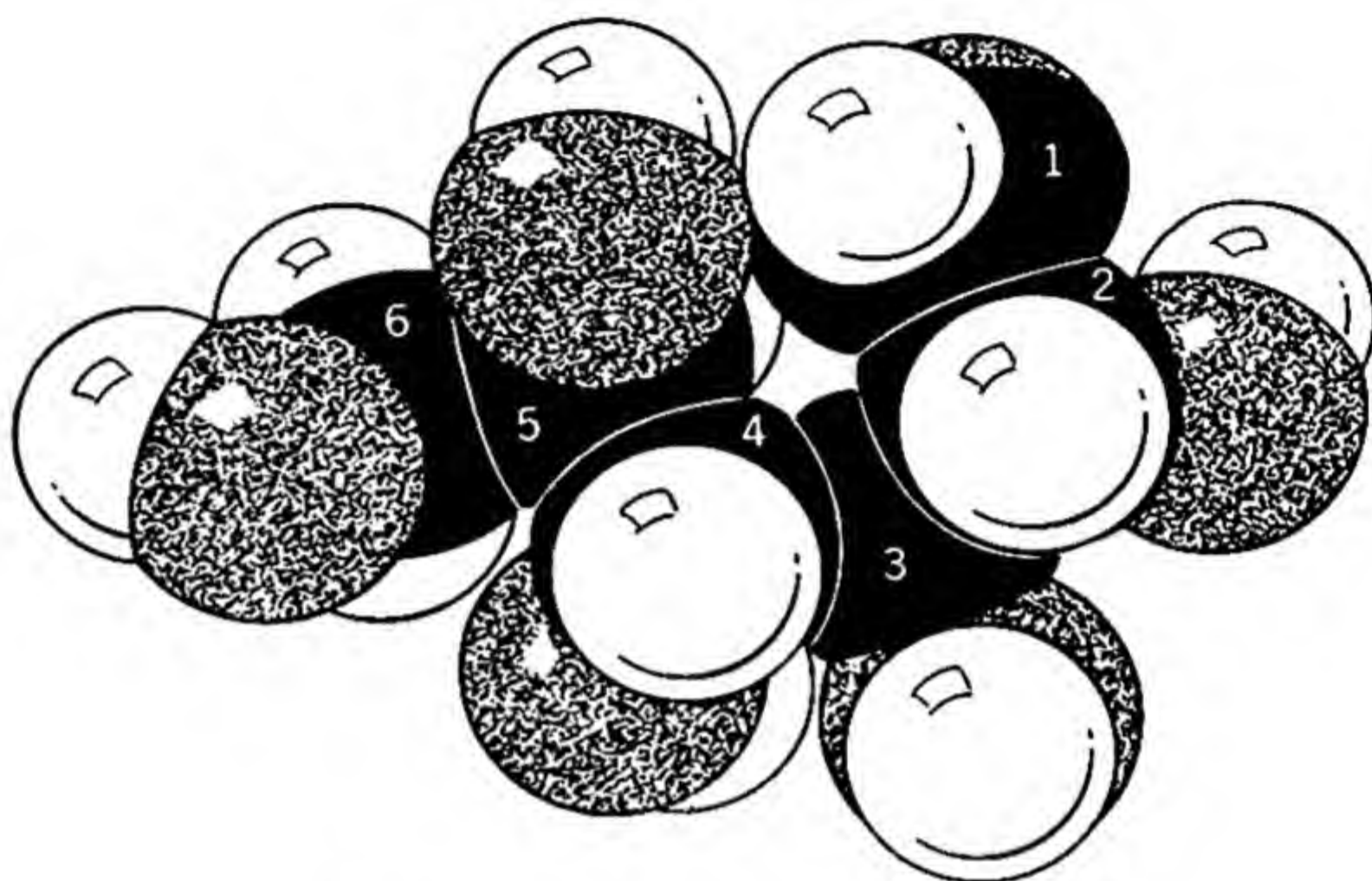
2. For each of the following structures state the number of optical isomers to be expected:



3. Racemic alcohols can sometimes be resolved by use of *l*-menthoxyacetyl



lution, using any racemic alcohol.



D-Glucose (open-chain form)

The “straight” carbon chain in D-glucose (and other monosaccharides) probably assumes the configuration shown in the model. The carbon atoms are numbered in the usual way (see p. 161). The proximity of the hydroxyl group attached to carbon atom 5 to the aldehyde group is well shown. It is the reaction between these two groups which leads to the formation of the cyclic structures of D-glucose.

The carbohydrates, fats, and proteins are the three great classes of foodstuffs. The carbohydrates are synthesized by plants from carbon dioxide and water and are oxidized by them for the production of energy. Animals are not able to manufacture carbohydrates but obtain them by ingesting plants and, like plants, produce energy by their oxidation. Cellulose, a complex carbohydrate, is synthesized by plants as a structural material.

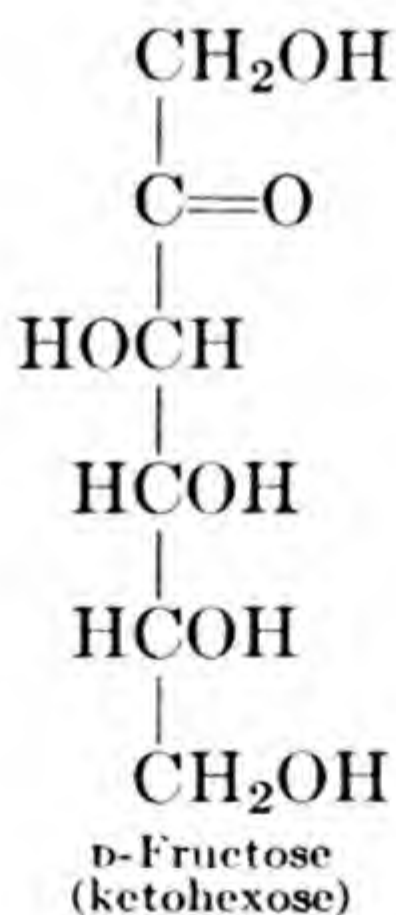


The name "carbohydrate" arises from an early assumption that these compounds are hydrates of carbon. This belief was supported by the fact that in the carbohydrates known at that time the ratio of hydrogen to oxygen atoms is 2:1, as it is in water, and by the fact that heating a carbohydrate produces water and leaves a residue of carbon.

Further investigation, however, showed that the carbohydrates have reactions characteristic of carbonyl compounds and also that they possess hydroxyl groups. Carbohydrates are now defined as polyhydroxy aldehydes or ketones, or anhydrides thereof, and are in part classified on the basis of this definition:

- I Monosaccharides
- II Disaccharides
- III Trisaccharides
- ⋮
- Polysaccharides

The monosaccharides correspond to the first part of the definition; that is, they are polyhydroxy aldehydes or ketones. They are said to be aldoses if they possess the aldehyde group, or ketoses if they possess the ketone group. They are also described as tetroses, pentoses, hexoses, etc., depending upon the number of carbon atoms in the molecule. These designations can be profitably combined to reveal both features of monosaccharide structure. Thus an aldopentose is a monosaccharide with an aldehyde group and five carbon atoms, and a ketohexose is a six-carbon monosaccharide with a ketone group.



Disaccharides give two monosaccharide molecules upon hydrolysis. In composition they may be considered to have two monosaccharide units which have been combined by the loss of a molecule of water.



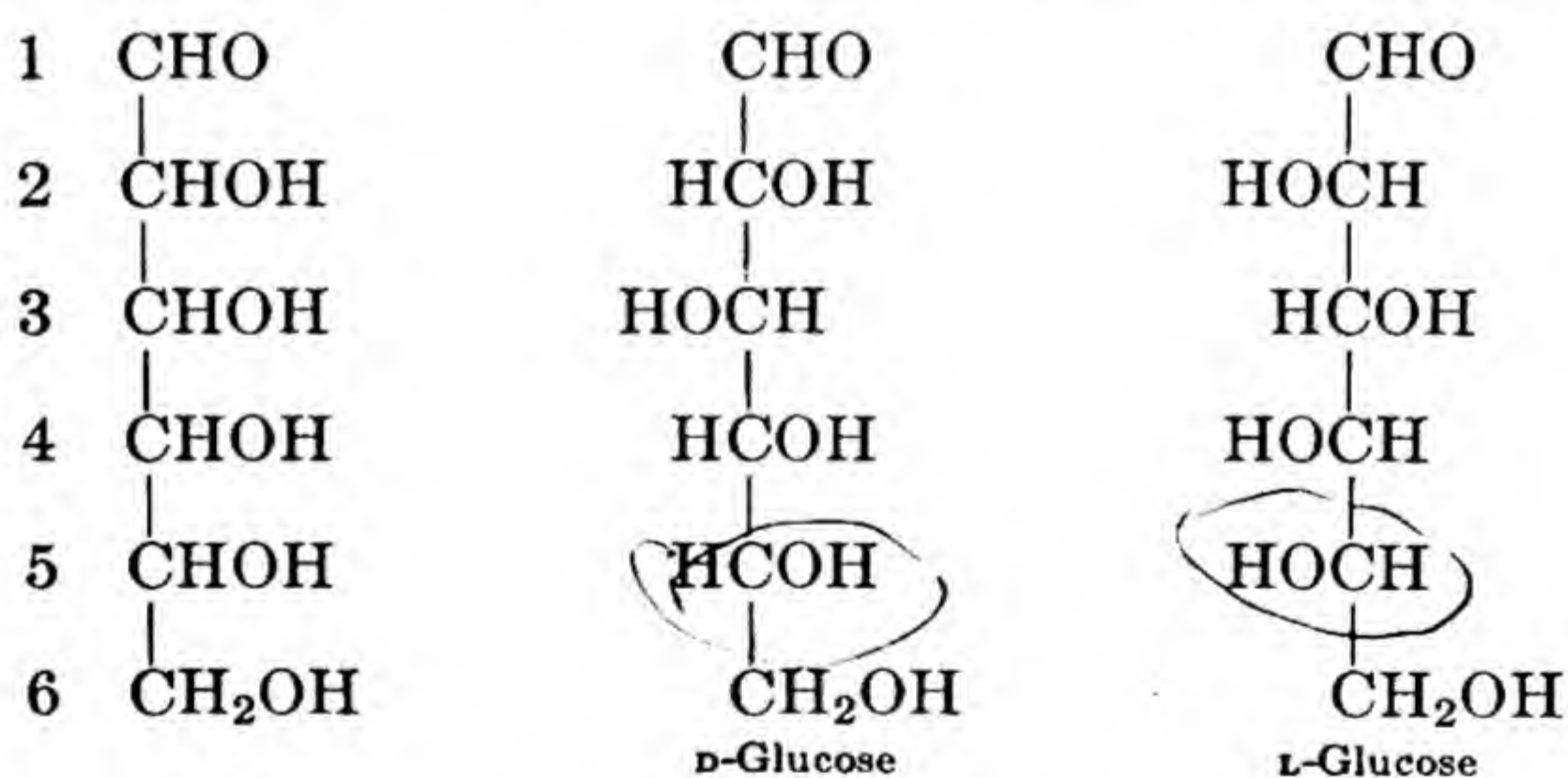
For example, a disaccharide of molecular formula  $C_{12}H_{22}O_{11}$  upon hydrolysis yields two  $C_6H_{12}O_6$  molecules. Thus disaccharides in a broad sense are anhydrides. The two monosaccharide units may be alike or different, and important examples of both types are known. The term "sugar" is a loose one which includes both mono- and disaccharides.

Trisaccharides are composed of three monosaccharide residues. Thus a trisaccharide  $C_{18}H_{32}O_{16}$  yields three  $C_6H_{12}O_6$  molecules upon hydrolysis. Trisaccharides are of relatively small importance.

Polysaccharides produce a large but inexact known number of monosaccharide units upon hydrolysis. Most polysaccharides, however, yield only one kind of monosaccharide. Starch and cellulose both furnish the monosaccharide glucose upon hydrolysis; they are said to be glucosans. Inulin, which occurs in the artichoke, is a fructosan. The ending "-an" signifies in general a polysaccharide, and the rest of the name specifies the monosaccharide unit.

## ► MONOSACCHARIDES

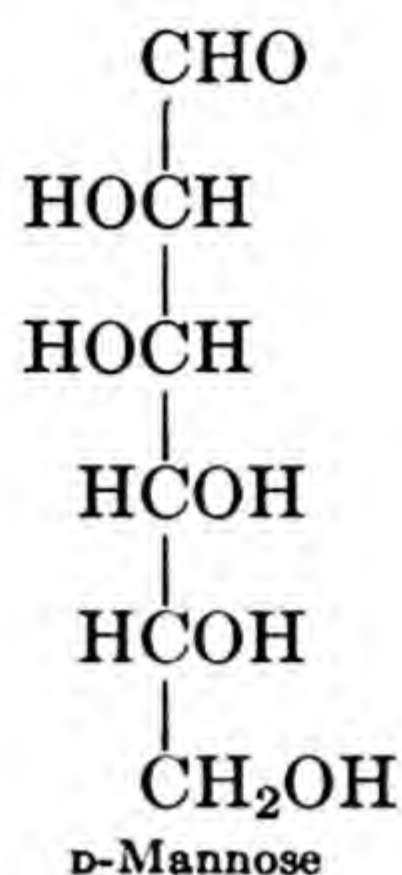
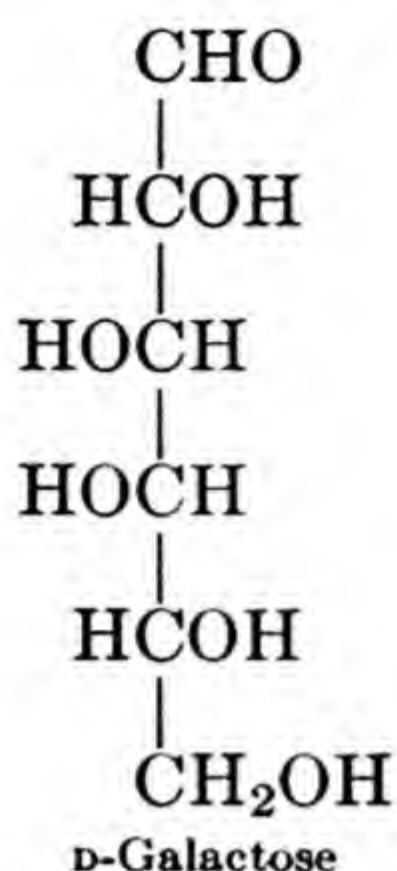
**Glucose.** The monosaccharide glucose (dextrose) is of very wide occurrence. It is found in plants and in the blood of all animals. Elemental analysis and molecular-weight determination show that glucose has the molecular formula  $C_6H_{12}O_6$ . Chemical evidence shows that its structure is that of an aldohexose. However, the aldo-



hexose formula has four asymmetric carbon atoms (2, 3, 4, and 5), and there are therefore sixteen possible optical isomers (all of which are known). One is the commonly occurring glucose (D-glucose). Its enantiomorph (L-glucose) does not occur naturally. Other aldohexoses of importance are D-galactose and D-mannose.

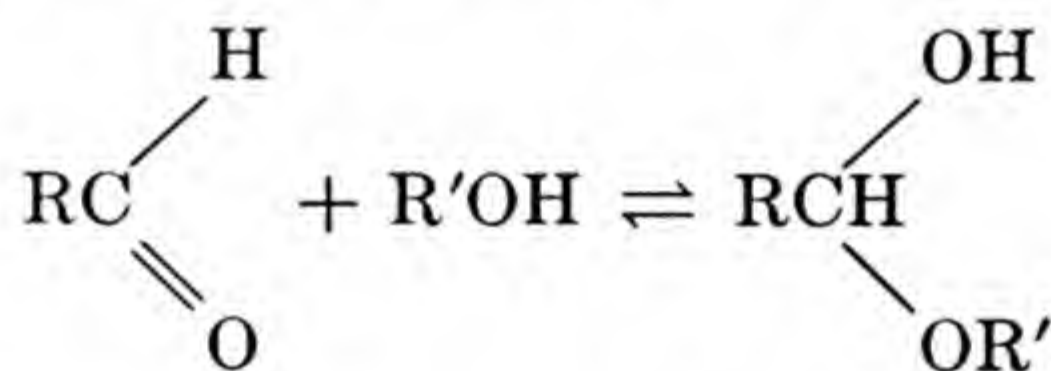


The small capital letters D- and L- prefixing the names of the sugars refer to the configuration at carbon atom number 5. In the com-



monly used convention the D indicates that the hydroxyl group is on the right-hand side in the projection formula. It is found advantageous to use these symbols in discussing carbohydrates, since it immediately reveals a portion of the configuration. The alternative, to use the prefixes *d*- and *l*- to indicate direction of rotation, is not particularly valuable, since no special significance attaches to the *direction* of optical rotation.

Recollection of the fact that aldehydes react with alcohols to yield hemiacetals would lead to the prediction that the aldohexoses would

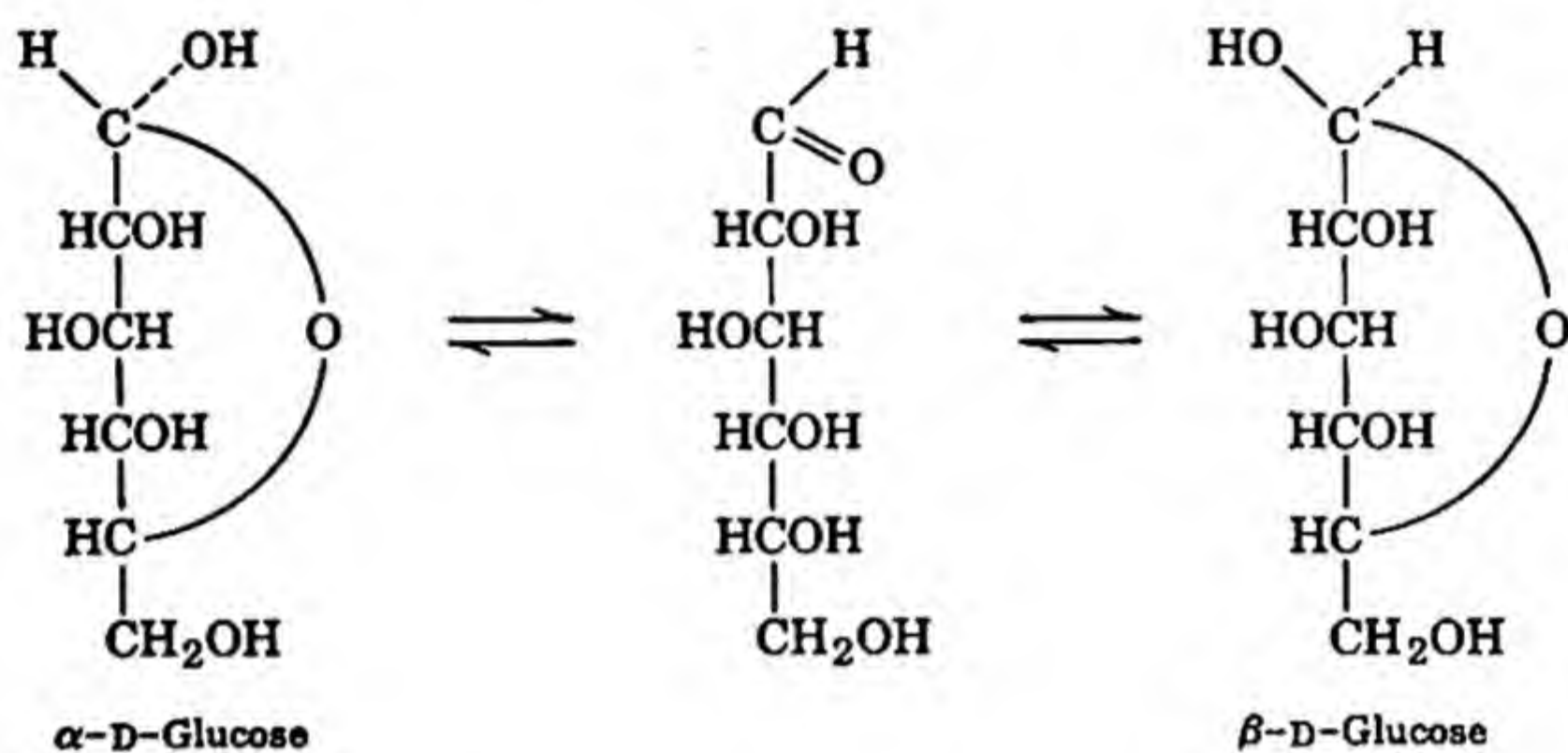


react internally, since both functional groups are present. Because there are five hydroxyl groups the possibilities are numerous, but it has been shown that the hydroxyl group attached to the number five carbon atom is the one which reacts. In the process the molecule becomes cyclic, and a new asymmetric carbon atom (formerly that in the aldehyde group) results. There are therefore two cyclic forms of D-glucose containing six-membered rings. These are designated as  $\alpha$ - and  $\beta$ -D-glucose. In the  $\beta$ -isomer the hemiacetal hydroxyl group extends forward from the number 1 carbon atom, whereas the hydrogen atom is behind it. The reverse is true of the  $\alpha$ -isomer.

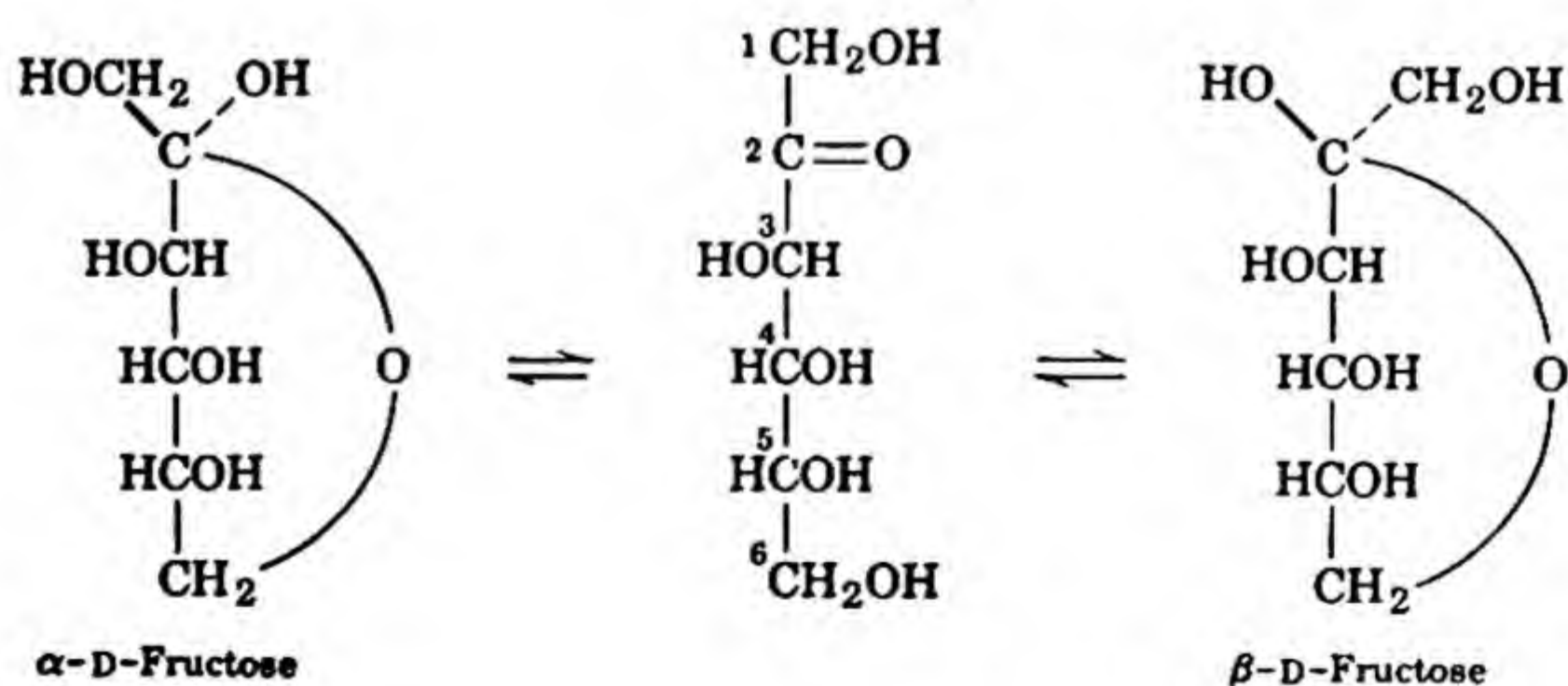
Because of the easy reversion to the open-chain structure D-glucose exists in water solution as an equilibrium mixture of the two cyclic structures and the open-chain form. Both cyclic compounds have



been prepared, and they can be made the subjects of an interesting experiment.  $\alpha$ -D-Glucose has a specific rotation in water of  $+113^\circ$ . If the solution is allowed to stand, the rotation diminishes until it reaches  $+52.3^\circ$ , where it becomes constant.  $\beta$ -D-Glucose has a specific rotation in water of  $+19^\circ$ . If its solution is allowed to stand, the specific rotation gradually increases until it reaches  $+52.3^\circ$ . It is believed that  $+52.3^\circ$  represents the optical rotation of the equilibrium mixture. This phenomenon, the gradual change in rotation of a freshly prepared solution of a compound to a constant value, is termed *mutarotation*.



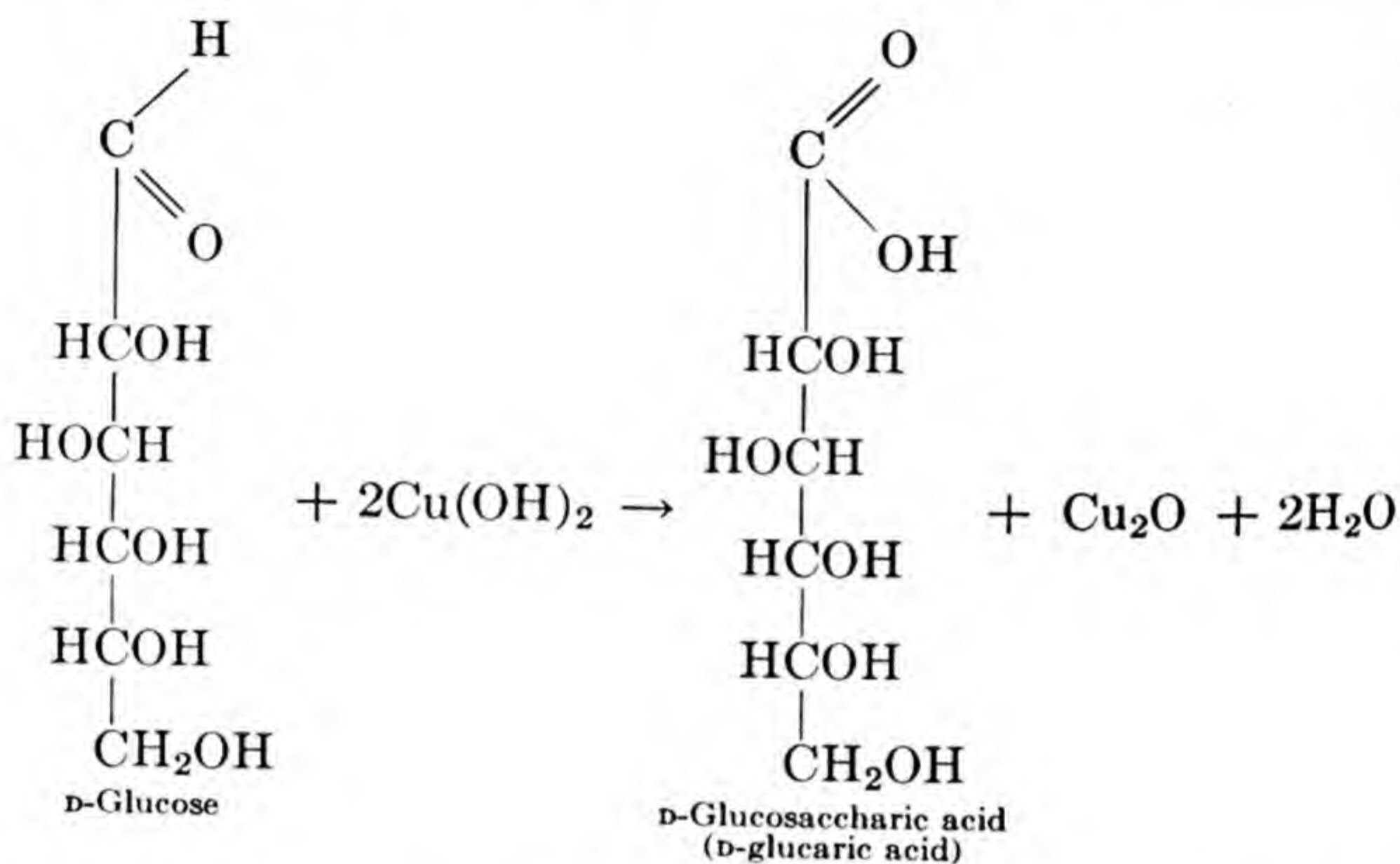
**Fructose.** D-Fructose (also called fruit sugar or levulose) is widely distributed in nature. Like glucose, it has the molecular formula  $C_6H_{12}O_6$ . It has a specific rotation of  $-93^\circ$ . By methods similar to those used for glucose it has been found that fructose is a pentahydroxy ketone. As with glucose, there are two cyclic hemiacetal structures having six-membered rings. An important point is that the three asymmetric carbon atoms of D-fructose (3, 4, and 5) have the same configurations as the corresponding ones in D-glucose.



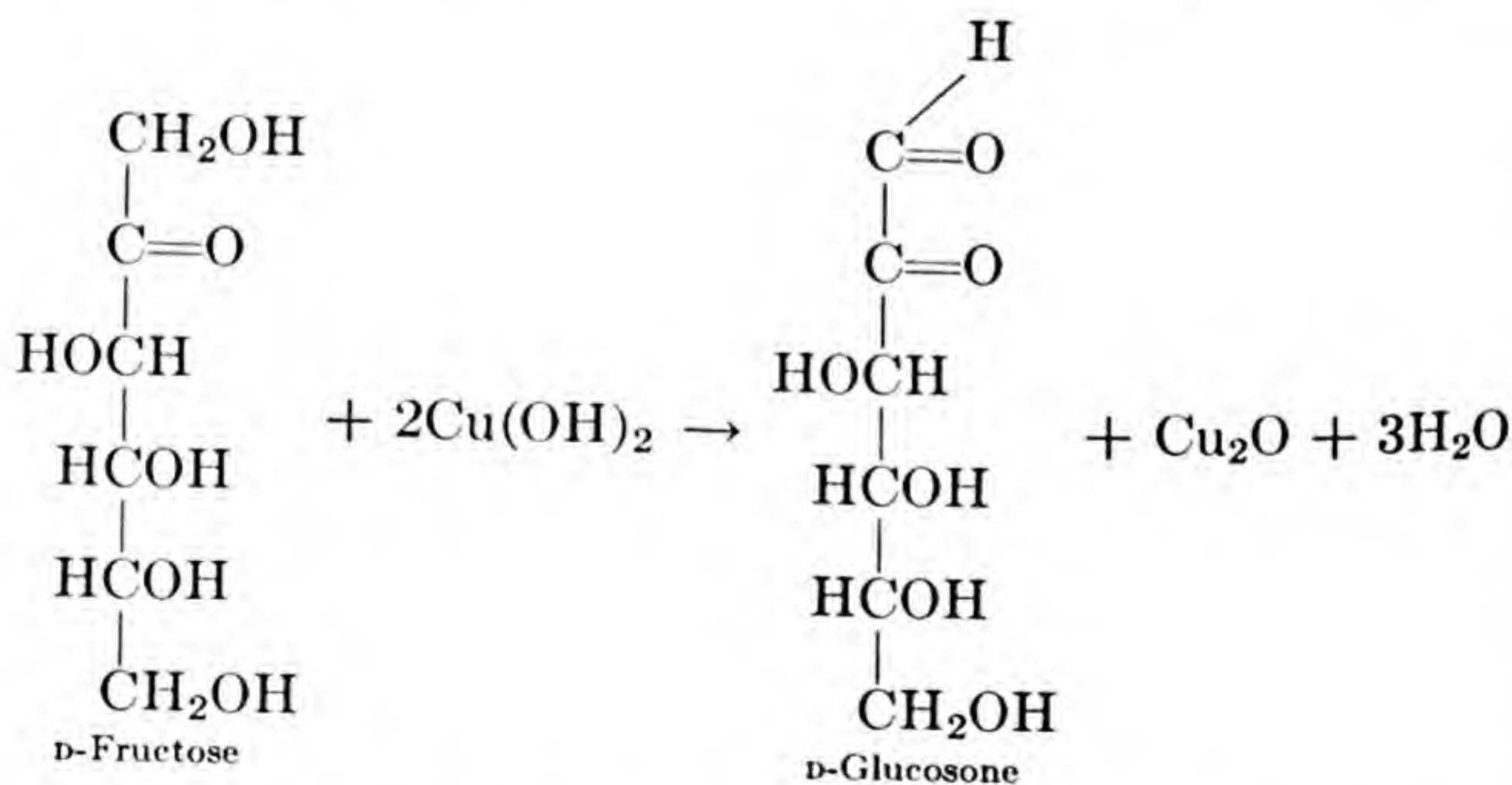


**Properties of the Monosaccharides.** The monosaccharides are white crystalline solids, soluble in water but not in organic solvents. They resist crystallization and are sometimes seen as viscous sirups.

The monosaccharides are readily oxidized. This property is utilized in the tests for these substances. The reagent commonly used is either Fehling's or Benedict's solution (Chapter 9). Perhaps sur-

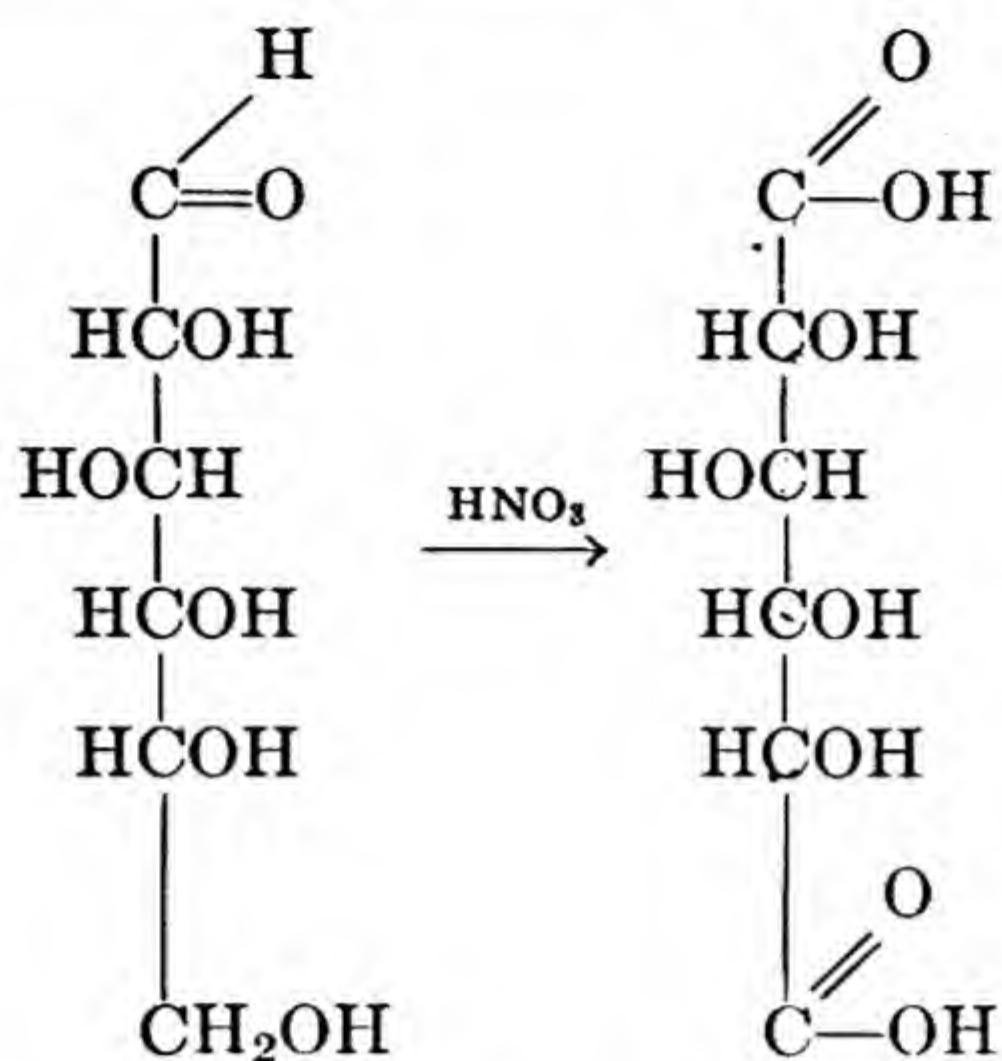


prisingly, ketoses are also oxidized by these reagents. The first product is a ketoaldehyde which may undergo further oxidation to an acid or cleavage of the chain. Fehling's or Benedict's test is

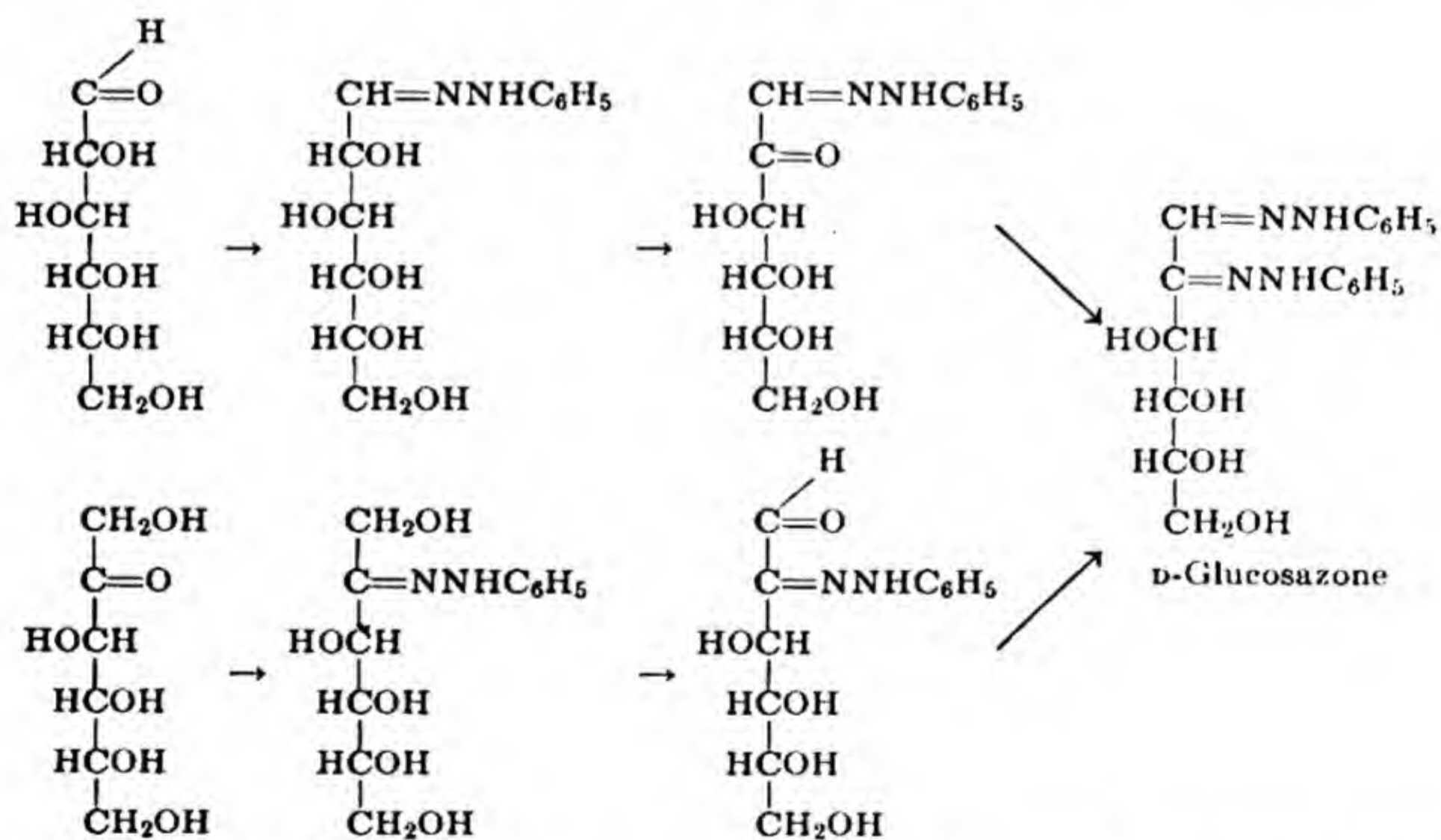


widely used to detect the presence of glucose in urine. A positive test may be indicative of diabetes.

More vigorous oxidation of the aldoses, using nitric acid, yields dibasic acids.



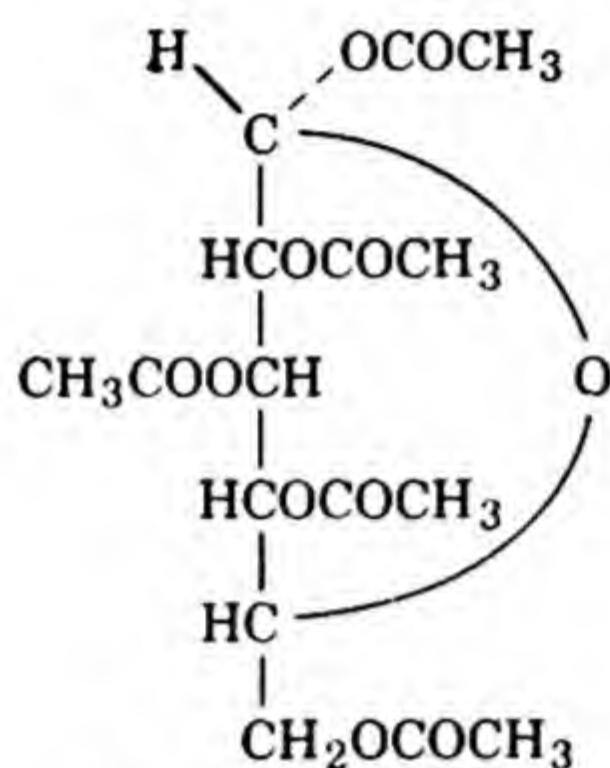
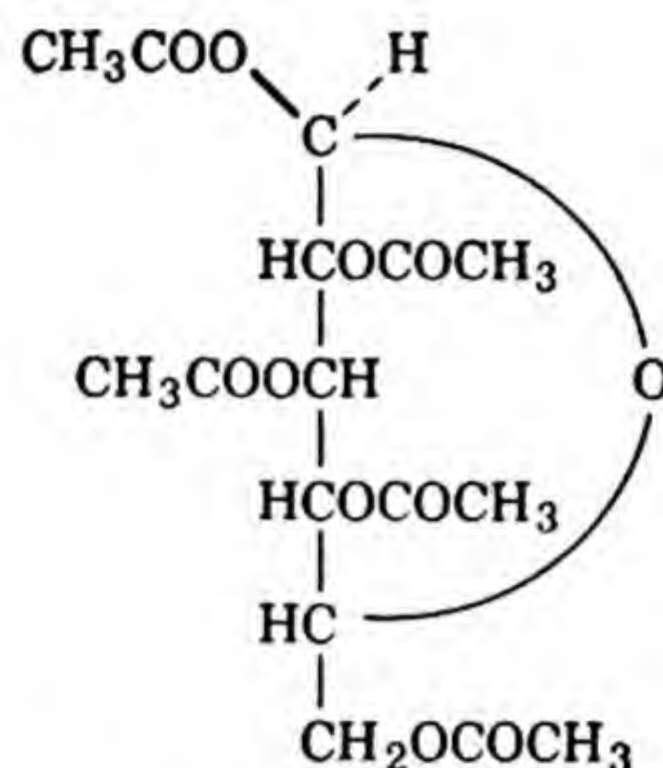
When monosaccharides are treated with sufficient phenylhydrazine they are converted into osazones. This is a very useful reaction because the osazones are beautifully crystalline derivatives which provide a means of detecting and identifying sugars. The formation of the osazones is usually written as occurring in three stages: production of the phenylhydrazone, oxidation of an alcohol group to give a new carbonyl group, and formation of the osazone. These changes are represented for D-glucose and for D-fructose.



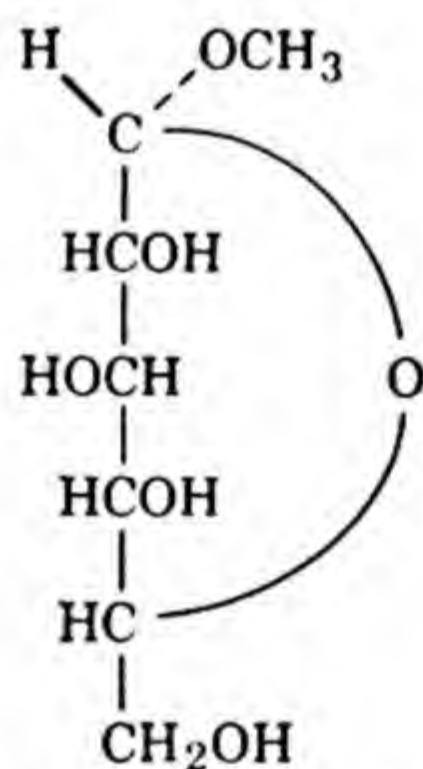
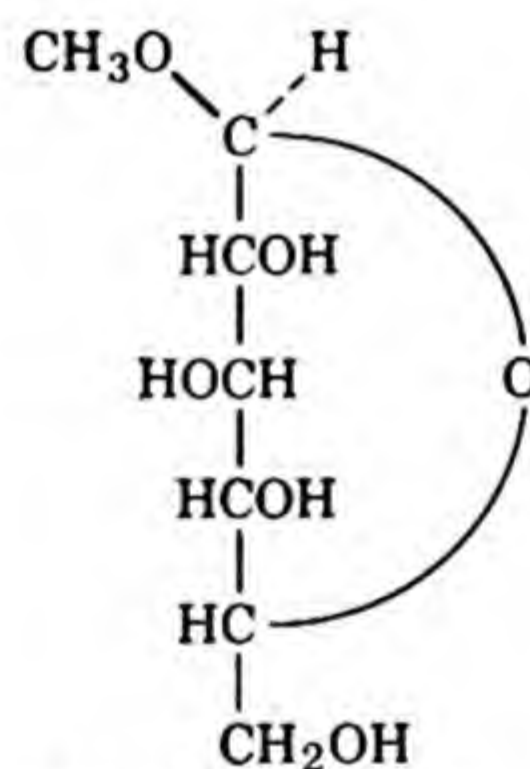
The two sugars give the *same osazone* because the configurations of carbon atoms 3, 4, and 5 are identical in them. The same osazone is produced by D-mannose. The only difference in the structures of D-mannose and D-glucose is in the configuration of carbon atom two. In the course of osazone formation the asymmetry of this atom is destroyed, so that the osazones of the two aldohexoses are identical.



The monosaccharides react with acetic anhydride under appropriate conditions to produce acetates. For example, D-glucose heated with acetic anhydride and sodium acetate yields two pentaacetates which correspond to the  $\alpha$ - and  $\beta$ -forms of D-glucose.

 $\alpha$ -D-Glucose pentaacetate $\beta$ -D-Glucose pentaacetate

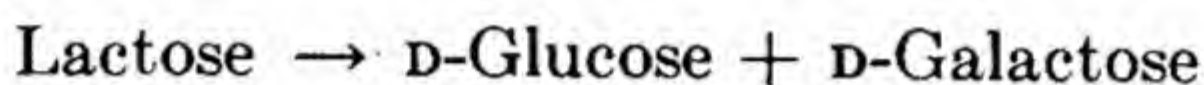
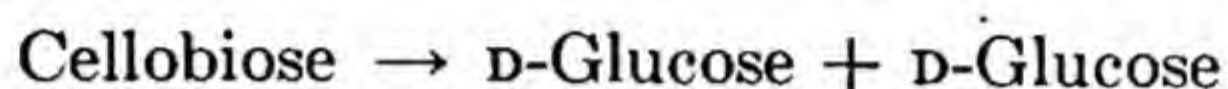
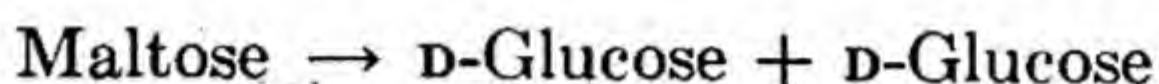
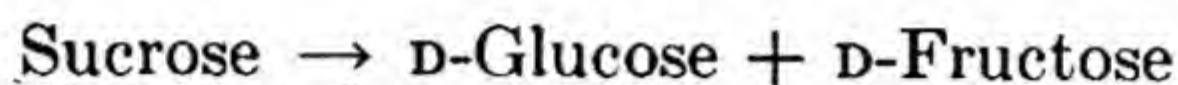
When the monosaccharides are treated with an alcohol and hydrogen chloride acetals are formed. With D-glucose as the example, these products may be written as shown below. The term glycoside

 $\alpha$ -Methyl-D-glucoside $\beta$ -Methyl-D-glucoside

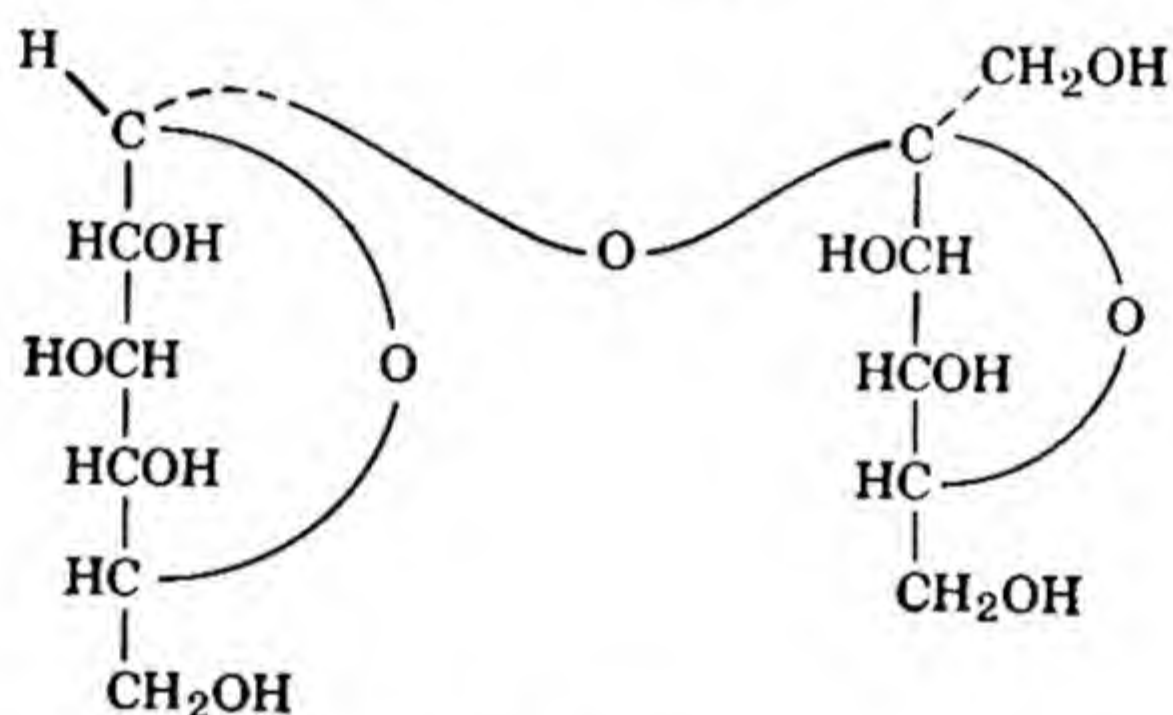
is used to describe this type of substance obtained from any sugar. Similar terms can be used to describe those from a particular carbohydrate, such as glucoside for glucose derivatives and galactoside for galactose derivatives. The glycosides are not readily hydrolyzed by water and therefore have no potential aldehyde groups. They do not react with Fehling's or Benedict's solutions or with phenylhydrazine. They can be hydrolyzed by aqueous acids to give the carbohydrate and the alcohol. Glycosides occur naturally, particularly in plants. The anthocyanins, which are plant pigments, are examples.

## ► DISACCHARIDES

A molecule of disaccharide produces two monosaccharide molecules on hydrolysis. All disaccharides of importance have the molecular formula  $C_{12}H_{22}O_{11}$  and give upon hydrolysis two monosaccharide molecules of molecular formula  $C_6H_{12}O_6$ . The common disaccharides and their hydrolysis products are represented below.



**Sucrose.** Sucrose is common table sugar. Nearly all the sucrose sold commercially is obtained from sugar beets and sugar cane. The mother liquor from the crystallization of cane sugar is called molasses; it contains considerable quantities of sucrose.



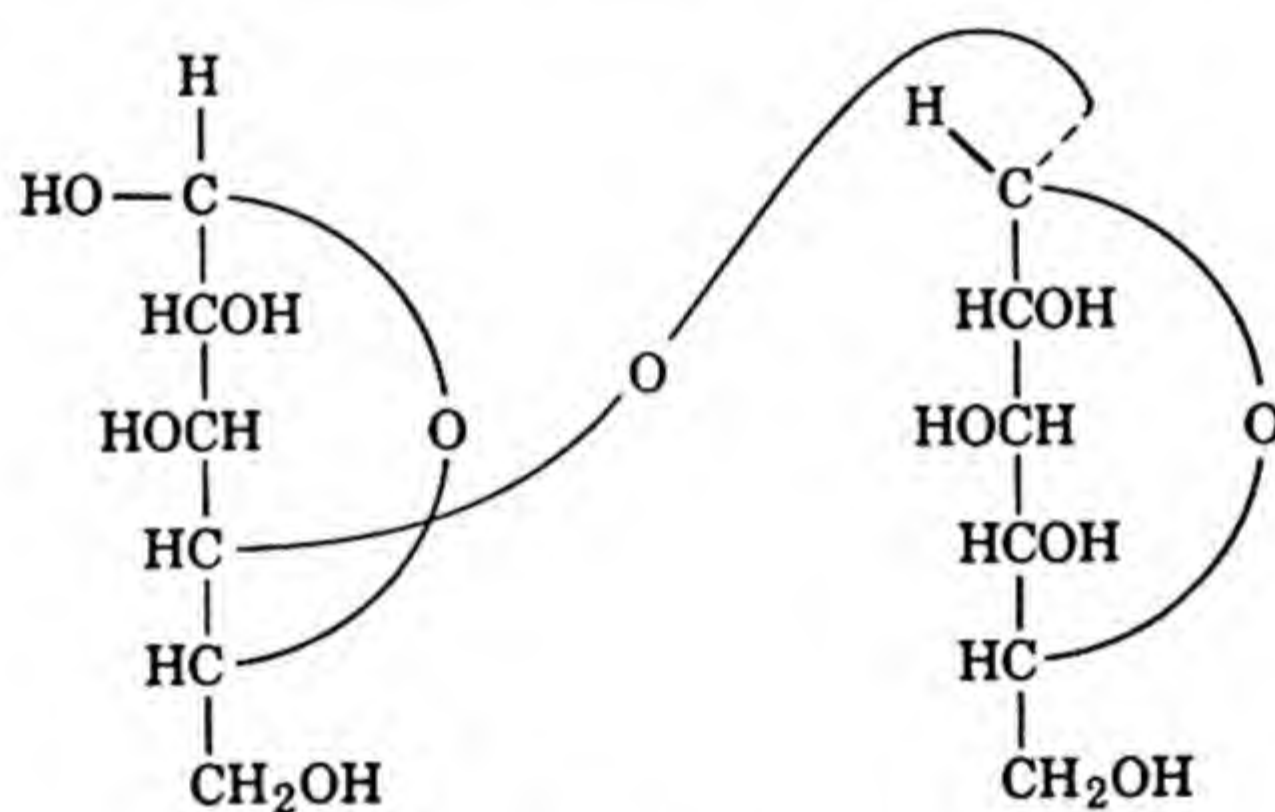
Sucrose

The hydrolysis of sucrose produces equal amounts of D-glucose and D-fructose. Sucrose is a nonreducing sugar; that is, it does not react with Fehling's solution, Benedict's solution, or similar oxidizing agents. Therefore sucrose does not possess a hemiacetal (potential aldehyde) group. Since glucose and fructose contain such groups, the two monosaccharide units in the disaccharide must be combined in such a way as to eliminate the hemiacetal groups. The hydrolysis of sucrose involves the addition of one molecule of water, and the conclusion is that the monosaccharide units are combined by the elimination of water between the two hemiacetal hydroxyl groups. Thus sucrose has an acetal group rather than a hemiacetal function and is not readily hydrolyzed by water alone. It may be considered both a glucoside and a fructoside. Other features of the sucrose



structure, such as whether the linkages are  $\alpha$ - or  $\beta$ - and the size of the rings in the monosaccharide units, have been determined by the chemical properties of the molecule. The fructose unit contains a five-membered ring (furanose) which is unusual, since it is often less stable than the six-membered (pyranose) ring. Sucrose has been synthesized.

**Maltose.** Maltose is produced when starch is hydrolyzed by an enzyme such as diastase in malt. It yields only glucose on hydrolysis. It is a reducing sugar, which shows that the union of the two glucose molecules does not involve both of the hemiacetal hydroxyl groups which derive from the aldehyde groups. Maltose is formed rather by the elimination of water between the hemiacetal hydroxyl of one glucose unit and an alcoholic hydroxyl of the other. Therefore, in addition to the acetal oxygen which joins the two monosaccharide units, a hemiacetal group remains free to give the characteristic reactions of the monosaccharides, such as oxidation by Benedict's or Fehling's solution, osazone formation, and mutarotation.



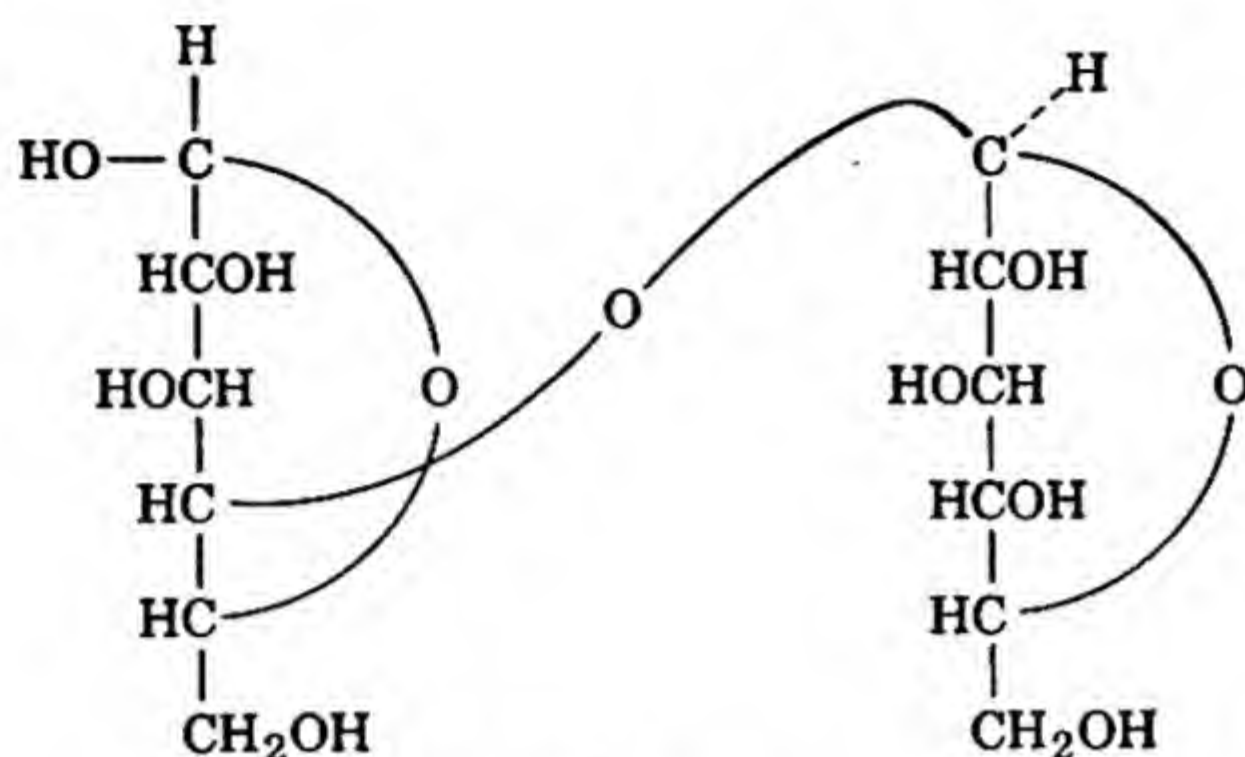
Maltose

It will be observed in the formula that the left-hand glucose unit contains the hemiacetal group, that the carbon atom number four is involved in the linkage to the other glucose unit, and that the right-hand glucose residue contains the acetal linkage and is an  $\alpha$ -D-glucose residue.

**Cellobiose.** Enzymatic hydrolysis of cellulose produces cellobiose. It thus bears the same relationship to cellulose that maltose does to starch. Like maltose, it yields two molecules of glucose on hydrolysis, and its chemical properties generally are quite similar to those of maltose. The only difference in the structures of the two disaccharides is that the linkage between the two glucose units in cellobiose is  $\beta$ . It is interesting that enzymes which hydrolyze  $\alpha$ -D-glu-

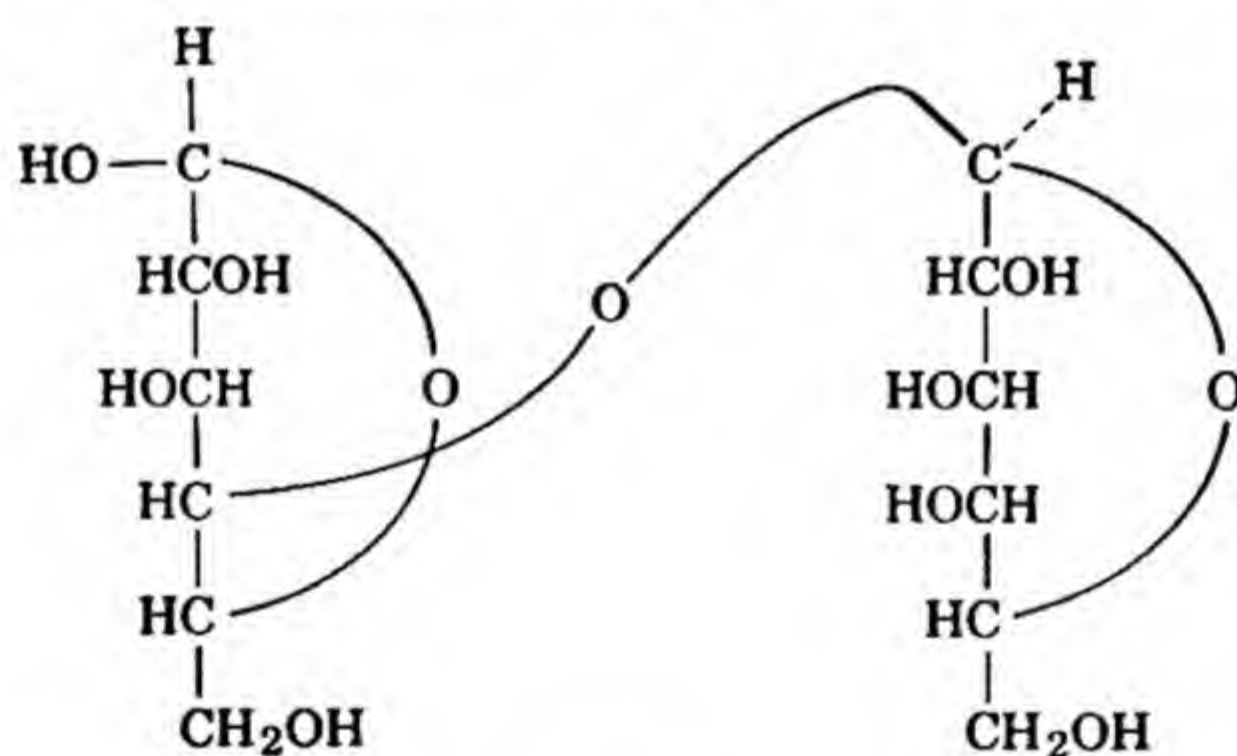


cose linkages will not hydrolyze  $\beta$ -linkages. Thus, though maltose is a food for all animals, only a few possess enzymes capable of catalyzing the hydrolysis of cellobiose.



Cellobiose

**Lactose.** Lactose is a reducing disaccharide with properties like those of maltose. About 3 to 5% is contained in the milk of mammals. The souring of milk is due to the formation of lactic acid by the action of certain bacteria upon lactose. Lactose is obtained as a by-product in the manufacture of certain cheeses, and hydrolysis yields equimolecular amounts of D-glucose and D-galactose.



Lactose

### ► TRISACCHARIDES AND TETRASACCHARIDES

Numerous trisaccharides have been described, the best known of which is raffinose, which occurs in sugar-beet liquors. It is a non-reducing trisaccharide and yields equal amounts of D-glucose, D-fructose, and D-galactose upon hydrolysis. A few tetrasaccharides have been found in nature. Stachyose, a nonreducing tetrasaccharide, yields two moles of D-galactose and one each of D-glucose and D-fructose when it is hydrolyzed.



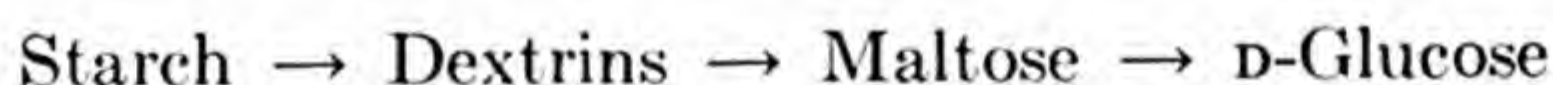
## ▶ POLYSACCHARIDES

The polysaccharides are substances of high molecular weight containing a large number of monosaccharide units. True polysaccharides produce only a single monosaccharide upon hydrolysis. The most important are the glucosans: starch, cellulose, dextrin, glycogen, and dextran. They differ from each other in molecular weight or in the mode of connection of the monosaccharide residues.

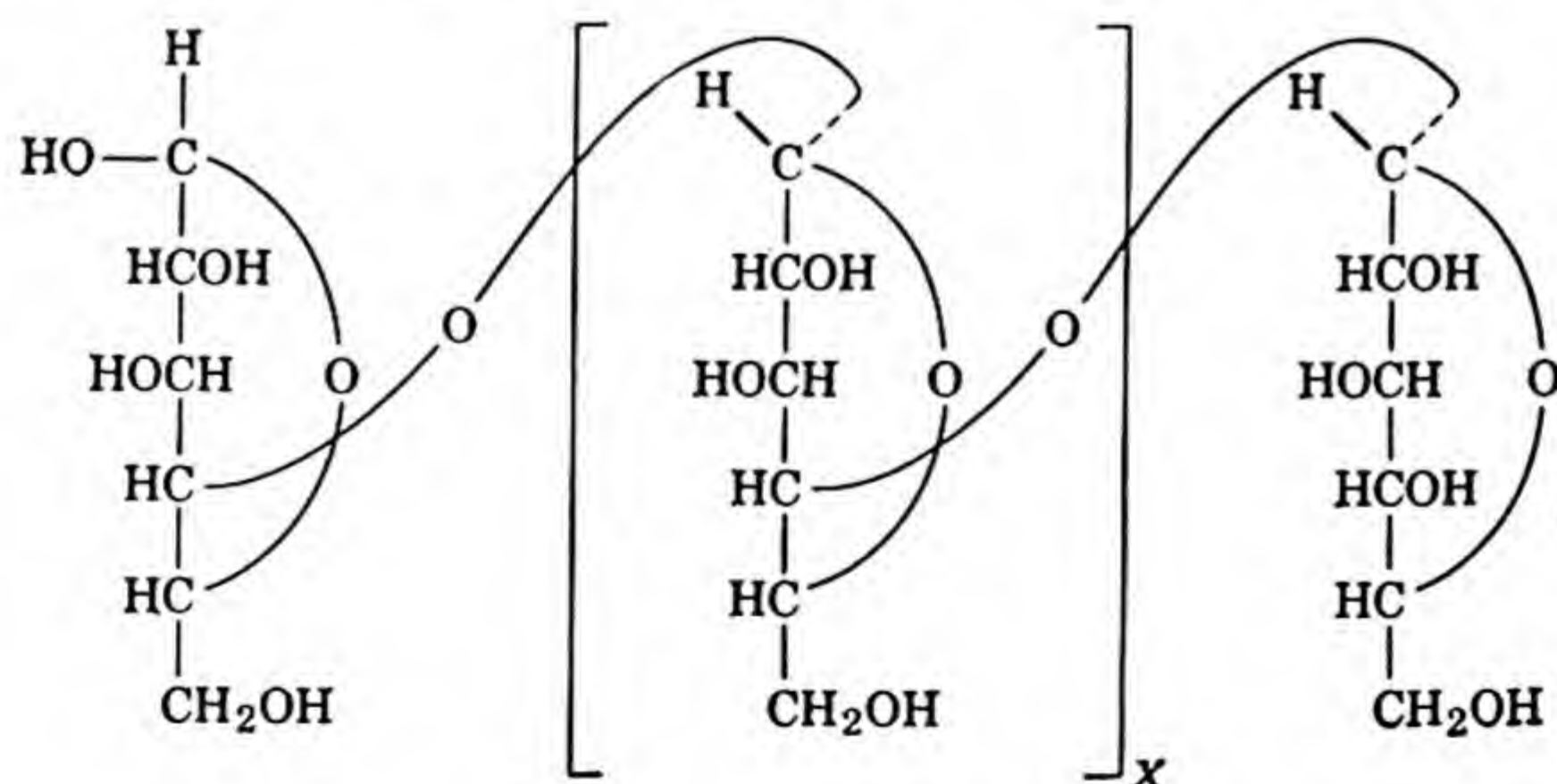
**Starch.** Starch is the storage form of carbohydrates in many plants and is therefore of wide occurrence. Starch sold commercially is obtained from corn, rice, potatoes, arrowroot, and other plants. These starches do not differ essentially from each other chemically, but the granules from various sources are sufficiently different in appearance to permit identification of the source.

An interesting property of starch is the intense blue color it gives with elemental iodine. This characteristic can be used for the detection of either starch or iodine. A modification of the test is used for oxidizing agents. The reagent is a mixture of starch and an iodide, and in the presence of an oxidizing agent the iodide is converted to free iodine, which, with the starch, produces the characteristic blue color.

Starch can be hydrolyzed by enzymes (the amylases) or by aqueous acids. The process consists essentially in the production first of smaller starchlike molecules, then maltose, and finally D-glucose.



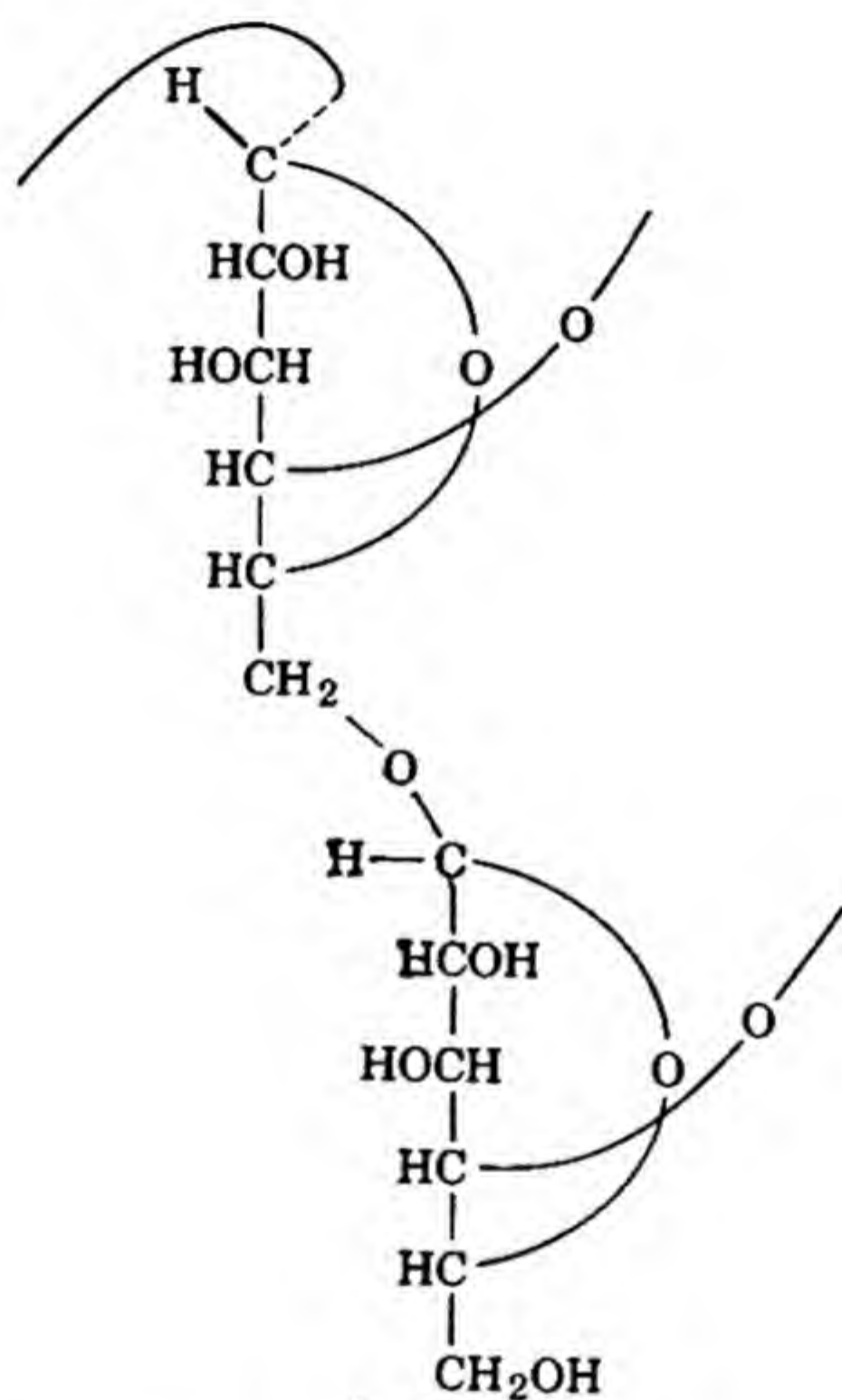
The progress of the hydrolysis can be followed partially by the iodine test. Depending upon their molecular weights, dextrins, with iodine, may give a blue, purple, or red color or none at all. The production of maltose in the hydrolysis indicates that starch is com-





posed of a large number of glucose units in which the connections are like those in maltose.

An important feature of the starch molecule is the occurrence of chains of about thirty glucose units joined as shown in the accompanying formula. However, starch itself is considerably more complex, for it contains a large number of such chains linked together. The mode of linkage of these chains to each other appears to consist in an acetal group formed by the reaction of the number 6 hydroxyl group with the hemiacetal group of an end unit. The total number of glucose units may be 5000.



Starches are widely used as foods; great quantities are consumed in grains, potatoes, and other vegetables. The hydrolysis of cornstarch under pressure with very dilute hydrochloric acid is the commercial process for manufacturing glucose. Interruption of the process at an early stage yields the mixture known as corn sirup. The enzymatic action of barley malt upon cornstarch can be made to produce a mixture of dextrans and maltose used as a baby food. Similar enzymatic action upon the starches of various grains to produce maltose is the first step in alcoholic fermentation.

Dextrans are also formed by heating starch. A common application of this transformation is the use of starch in laundries; the hot iron passes over the starch and converts it to dextrans which adhere to



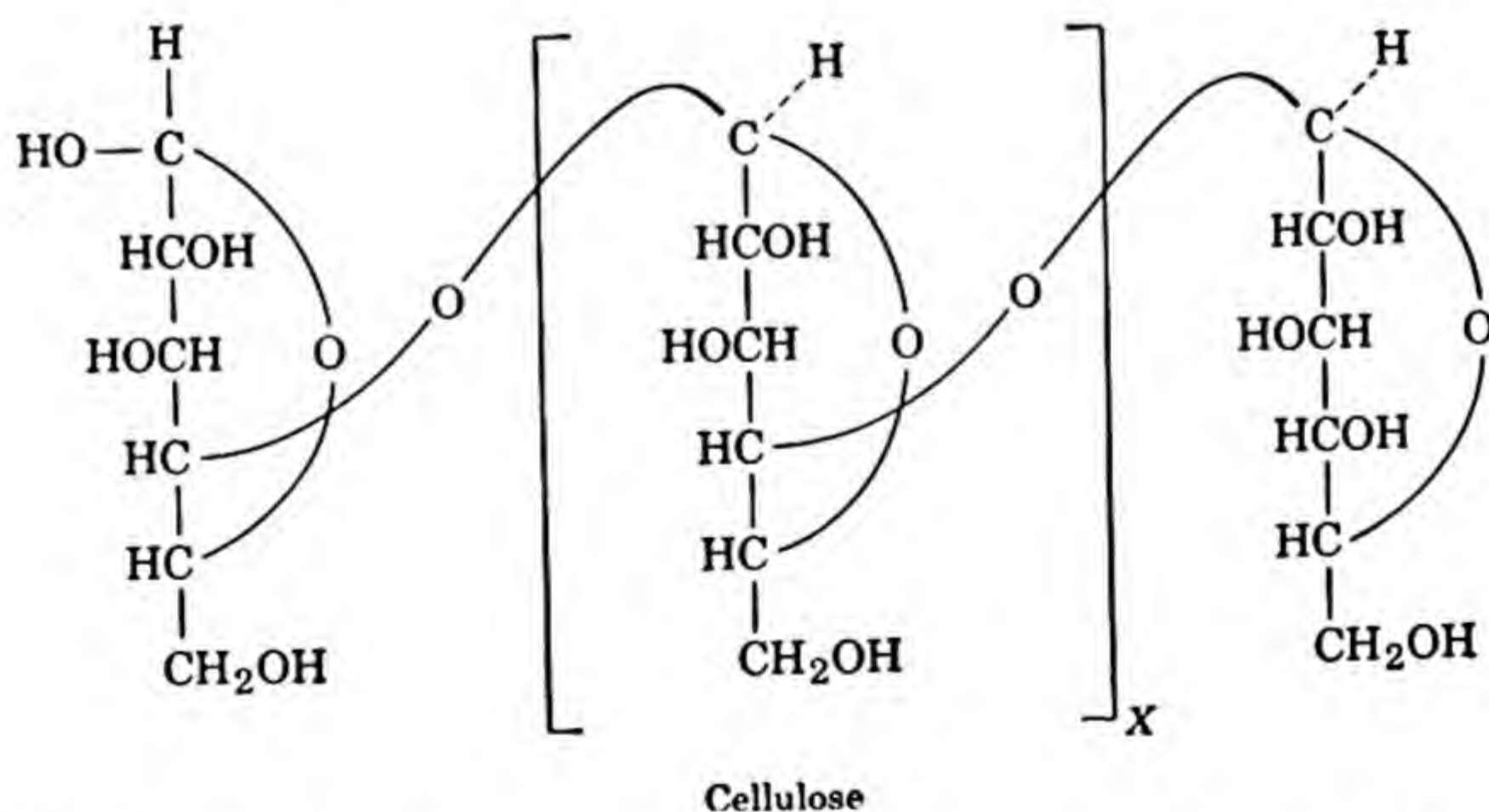
the cloth. These dextrans are stiff and shiny and are responsible for the glossy appearance of starched fabrics. Dextrans are sticky when wet and are used in manufacturing mucilage for postage stamps.

**Glycogen.** Glycogen, sometimes known as animal starch, is the storage form of carbohydrates in animals. As such, it is found in the muscles and liver. An adult human can store about 200 grams in each of these places, or a total of somewhat less than a pound.

Glycogen is a polymer of  $\alpha$ -D-glucose and is similar therefore to starch and dextrans. Glycogen samples vary greatly in molecular weight, and their structures appear to be highly branched. Glycogen gives a red color with iodine.

**Dextrans.** The action of certain microorganisms upon sucrose produces dextrans which are D-glucosans. They have relatively low molecular weights but appear to be rather complex structurally. Dextrans are used as blood extenders; that is, a given amount of blood plasma can be diluted with a dextran solution to give a larger volume which is a suitable plasma substitute.

**Cellulose.** Cellulose occurs in all plants, where it serves as a structural material in the cell walls. It is a D-glucosan, but the units are linked in the  $\beta$ -fashion. The molecular weight of cellulose is difficult to determine because the chemical or physical treatments which are necessary cause change in the molecule. It is likely, however, that cellulose contains at least 3000 glucose units; this corresponds to a molecular weight of about 500,000.



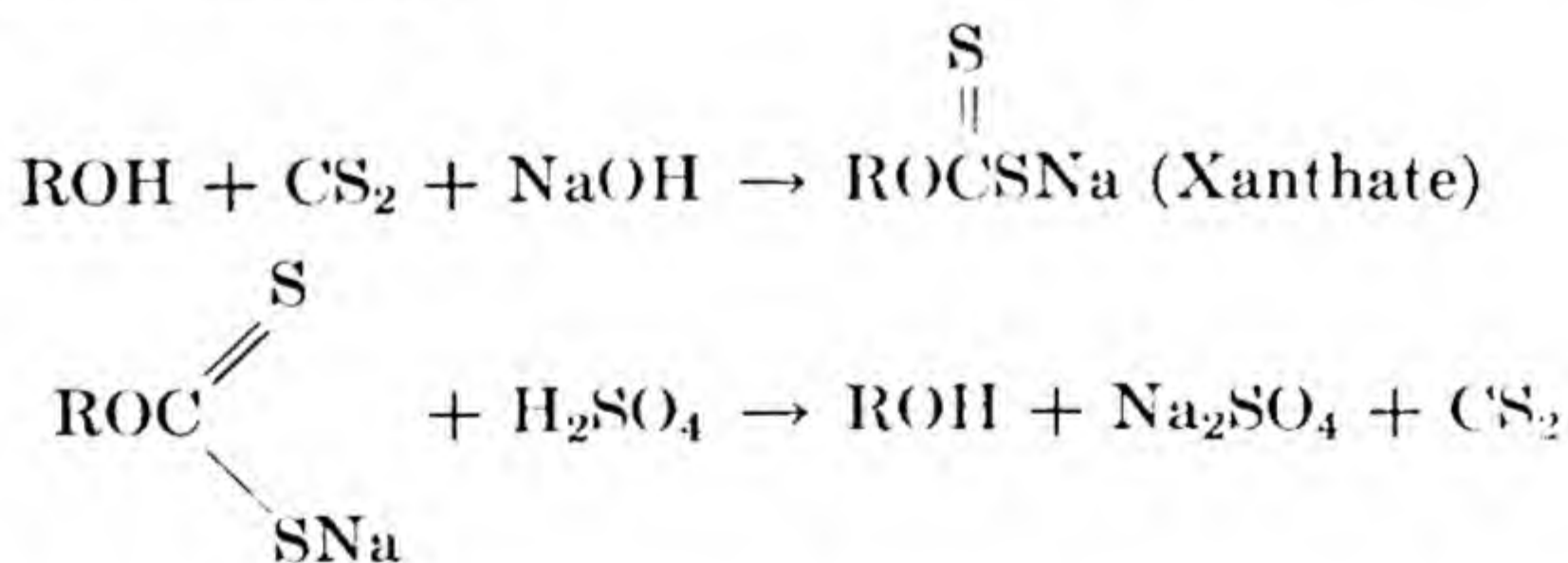
The hydrolysis of cellulose to glucose can be accomplished by acid or by enzymatic catalysis. The digestive system of man, however, is unable to hydrolyze cellulose, and therefore it is not a food for humans.



Though straw, seed hulls, and other materials can be used for making cellulose commercially, the chief sources are cotton, linen, and wood. Cotton is nearly pure cellulose; the natural fiber is covered with a small amount of waxy material which makes the fibers waterproof. If the waxy coating is removed with a solvent, the fibers will take up water. This is known as absorbent cotton. Linen, obtained from flax straw, is a less pure form of cellulose. The contaminants are removed by soaking in water, a process called retting.

In addition to cellulose, wood contains a large amount of lignin, a substance of unknown structure. In the manufacture of paper from wood the first step is the removal of the lignin. The quality of the paper depends in part on the completeness of this process. Higher quality papers are made from linen or cotton rags. Writing papers also contain a "sizer," such as rosin, glue, starch, or silicates, which prevents the ink from spreading. Parchment paper is made by dipping ordinary paper into cold concentrated sulfuric acid. It has a hard surface which is impervious to water.

**Regenerated cellulose.** Cotton fibers are short and irregular, compared with those of silk, which are long, tubular threads. This difference in the physical characteristics of the fibers accounts for the difference in the appearance of cotton and silk. Viscose, the common type of rayon, is made by changing the physical form of cellulose so that uniform tubular fibers are produced. The cellulose is dissolved in a mixture of carbon disulfide and sodium hydroxide. The solution thus produced is forced through very fine openings into a bath containing sulfuric acid, which converts the cellulose derivative back to cellulose. The reactions upon which the process depends are the following:

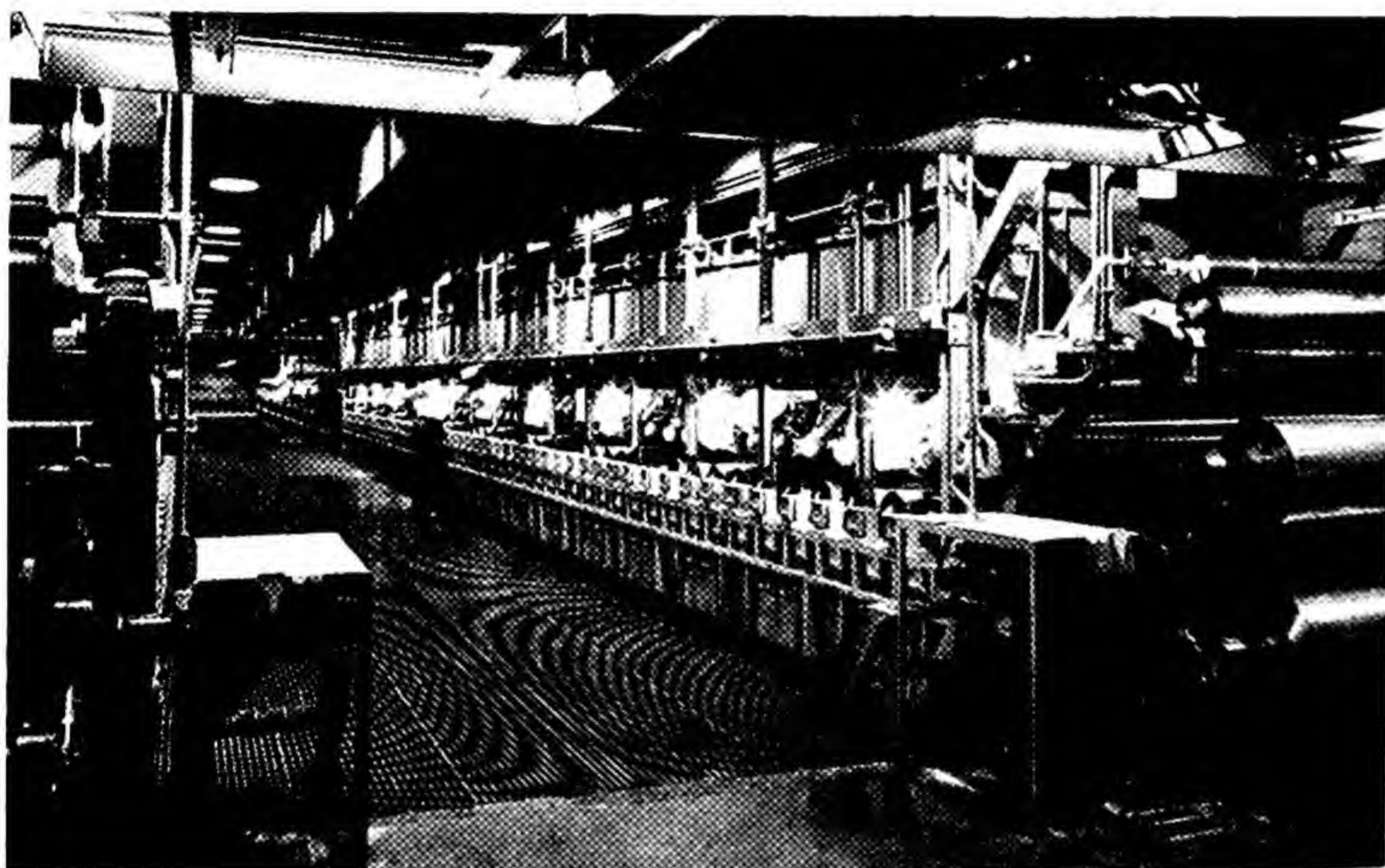


Cellulose contains numerous hydroxyl groups, many of which undergo the reaction indicated. The solution of the xanthate, which is yellow and viscous, is allowed to stand for a time before regeneration. The fine filaments produced are twisted together to form rayon yarn. For most viscose rayon wood cellulose is used as the



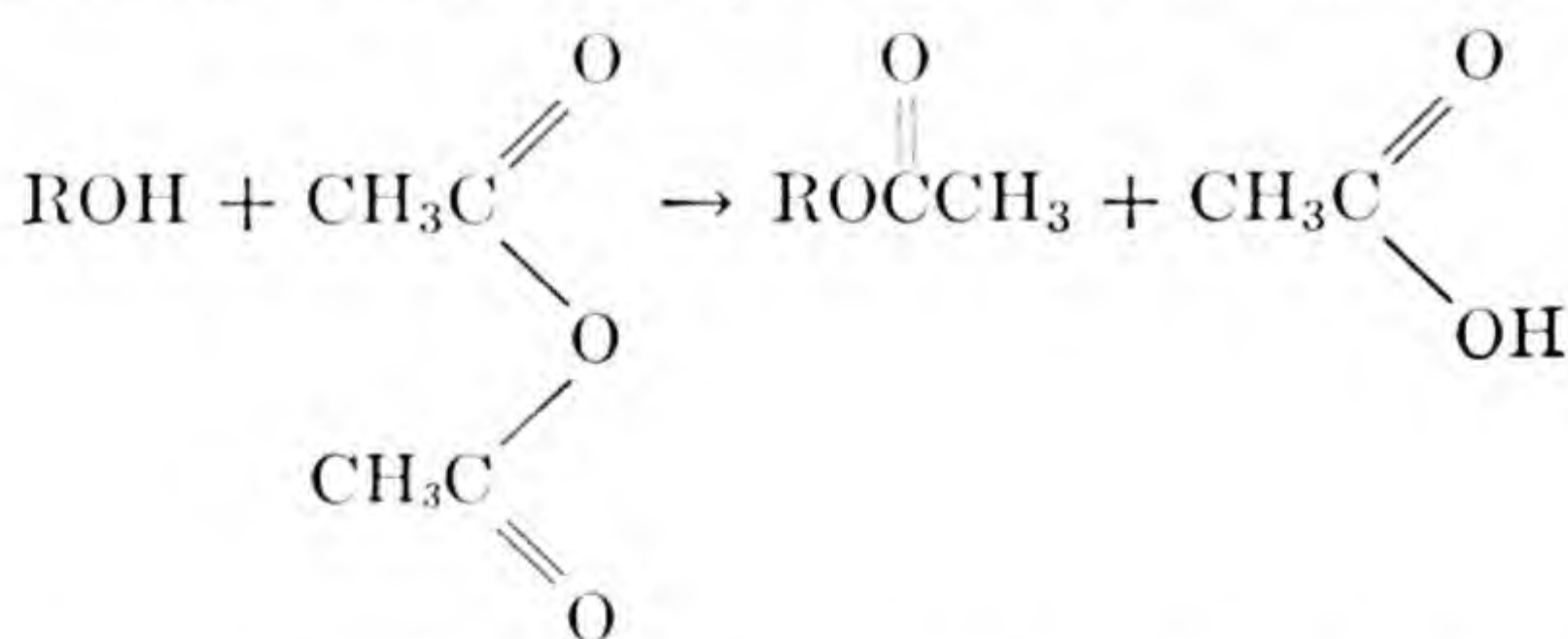
starting material. Cotton linters yield a somewhat stronger rayon which is used in tire cord.

If the viscose solution is forced through slits instead of holes, a thin continuous sheet results. This material, called cellophane, is plasticized by the addition of glycerol or other materials and is made moistureproof by coating it with a very thin layer of a moisture-resistant plastic.



A 200-foot long cellophane casting machine. The viscose solution enters at the far end where the cellophane is precipitated in an acid bath. Washing, softening, and drying processes follow, and the finished film is wound on rolls at the near end of the machine. (Photograph courtesy of the Du Pont Company.)

**Cellulose acetate.** Cellulose reacts with acetic anhydride to give cellulose acetate. Since each glucose unit of cellulose has three



hydroxyl groups, the so-called triacetate is produced. The usual commercial products have fewer than three acetate units per glucose



residue; they are obtained by partial hydrolysis of cellulose triacetate. Some degradation of the cellulose molecule occurs in the acetylation and hydrolysis processes, so that the cellulose acetates have lower molecular weights than the original cellulose.

Cellulose acetate fibers can be made by forcing a solution through small orifices into a chamber where the solvent is evaporated. The fibers are woven into a cloth called acetate rayon or "acetate." Cellulose acetate is also used for motion-picture film and as wrapping film and can be molded by heat and pressure into various shapes.

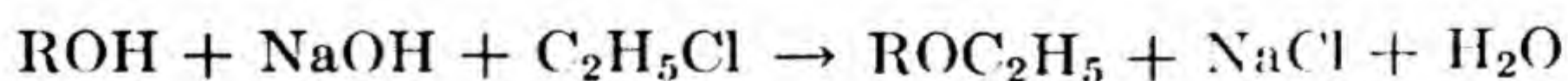
**Cellulose nitrate.** Nitric acid reacts with cellulose in the presence of sulfuric acid to give cellulose nitrates. The term is applied to a wide variety of products having different properties and differing in the degree of nitration. Complete nitration would be expected to give the trinitrate  $[\text{C}_6\text{H}_7\text{O}_2(\text{ONO}_2)_3]_x$  containing 14.14% nitrogen. Guncotton has 13.0% nitrogen or more, whereas cellulose nitrates used for plastics and similar applications have less than 12.5%.

Cellulose nitrates are highly inflammable, a property which to some extent dictates their uses. Guncotton is used as a propellant. In its manufacture cellulose nitrate of high nitrogen content is swollen with a solvent to form cylinders called grains. The size of the grain varies with the gun for which it is to be used. For a 75-mm gun they are 10 mm long and 3 mm in diameter, and for a 16-inch gun they are 58 x 24 mm.

Celluloid is a mixture of pyroxylin, a lower-nitrated cellulose, and camphor. Its use has decreased considerably with the production of new plastics. A solution of pyroxylin in ether and alcohol is called collodion. It was formerly used in protecting wounds but is now employed chiefly for the protection of labels, printing, stencils, etc. Lacquers are similar to collodion but contain a solvent such as butyl acetate which evaporates more slowly. Lacquers also contain gums, resins, plasticizers, and pigments.

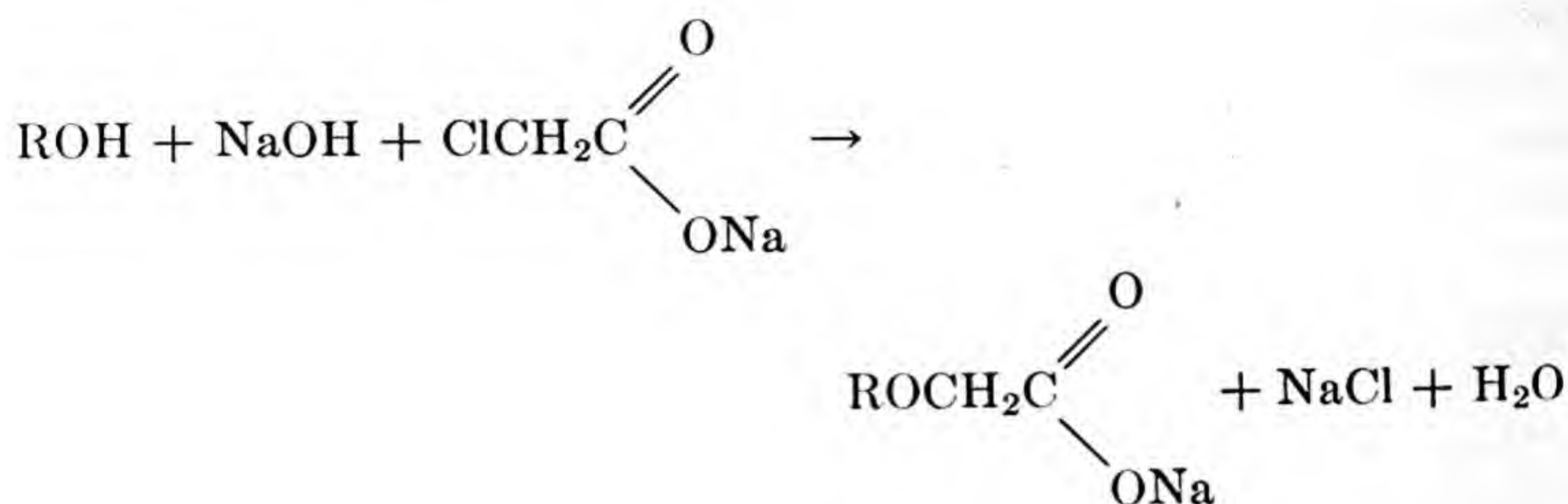
Cellulose nitrates are used in the manufacture of motion-picture film, particularly that used commercially, toecaps in shoes, grease-resistant coatings, and adhesives and cements.

**Other cellulose derivatives.** Cellulose acetate butyrate, in which some of the hydroxyl groups of cellulose are esterified with acetic acid and some with butyric acid, is used in the manufacture of "plastic" objects and in lacquers. Ethylcellulose, similarly used, is an ether of cellulose made by the reaction of cellulose with sodium hydroxide and ethyl chloride.



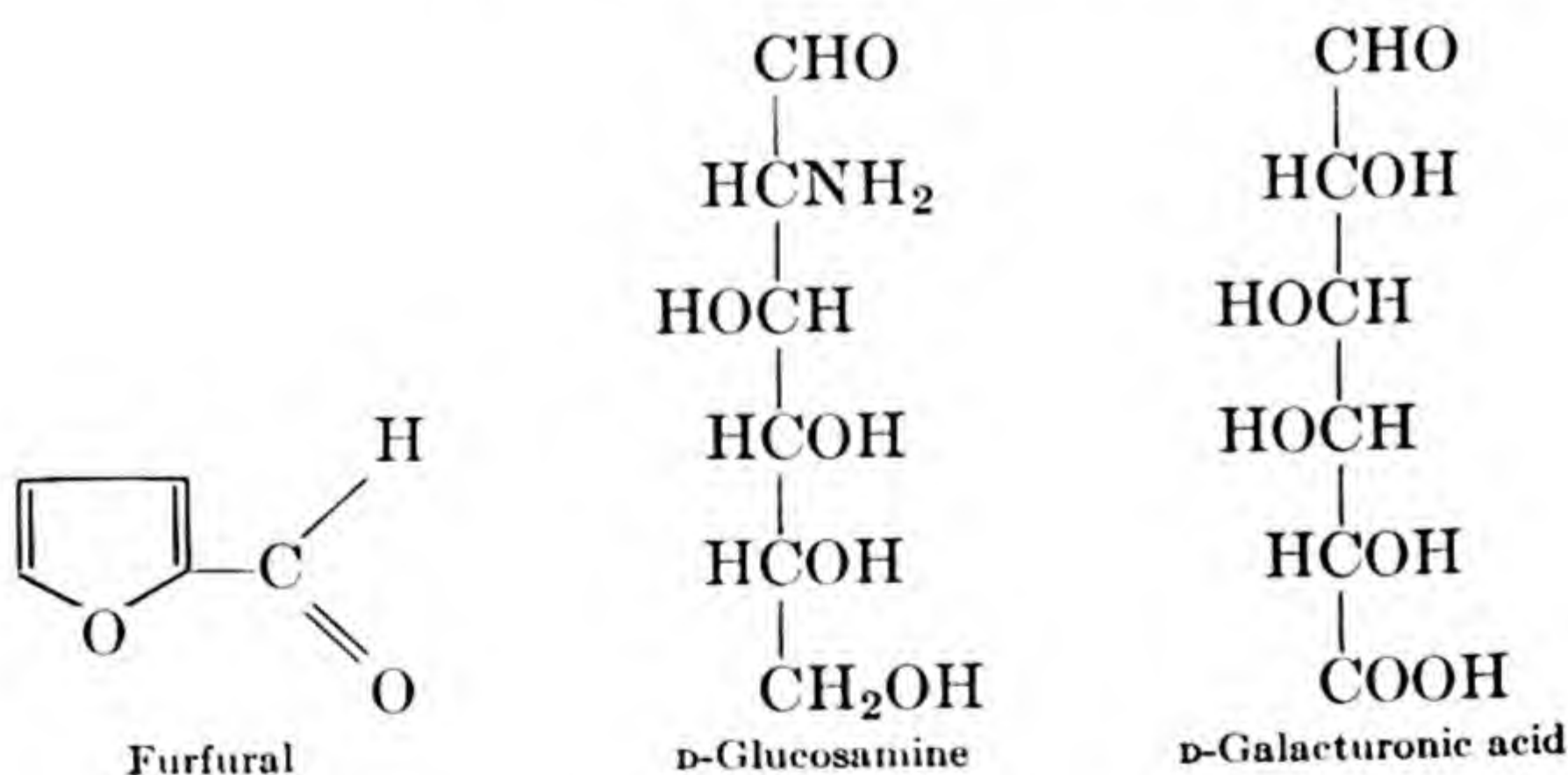


Carboxymethylcellulose is made by the reaction of cellulose, sodium hydroxide, and chloroacetic acid.



It is ordinarily employed as the sodium salt which is soluble in water. Even dilute solutions are viscous. Carboxymethylcellulose is used as a thickener in foodstuffs, such as ice cream and other frozen confections, in printing pastes for fabrics, and in wallpaper paste.

**Other Polysaccharides.** A number of polysaccharides other than glucosans occur naturally. Inulin, a fructosan, occurs in the artichoke. Pentosans are found in the cell walls of plants and can be obtained in especially large amounts from cereal straws, corn cobs, and oat and cottonseed hulls. When they are hydrolyzed with acid the pentosans yield furfural, a heterocyclic aldehyde. Furfural is used in petroleum refining and in the manufacture of nylon intermediates. Chitin is a polymer of D-glucosamine. It forms a part



of the hard shell of crustaceans, such as crabs and lobsters, and of many insects. The units are probably linked together in the same way as the D-glucose units in cellulose. Pectins, which are obtained from various fruits, are mixtures of galactans or arabans with pectic



acids, which are polymers of D-galacturonic acid. The pectins have the property of forming gels with water and on this account are used in the manufacture of edible jellies and the like. The gums are also polysaccharidelike materials, but their structures are more complex. Upon hydrolysis they produce three or four different carbohydrates or carbohydratelike compounds. The gums yield stable emulsions in water and are widely used in the pharmaceutical and cosmetic industries.

## ✓ ► **DIGESTION AND METABOLISM OF CARBOHYDRATES**

Of the large number of known carbohydrates only a few can be digested by man. These include the monosaccharides glucose, galactose, and fructose, the disaccharides sucrose, maltose, and lactose, and the polysaccharides starch, dextrans, and glycogen. Other carbohydrates which are ingested, such as the pentosans, are excreted as such.

Some digestion of carbohydrates occurs in the mouth. Ptyalin, an enzyme, catalyzes the hydrolysis of starch to maltose and low-molecular-weight dextrans. Though the stomach acts primarily as a storehouse for food, some digestion occurs through the agency of ptyalin carried over from the mouth. The remainder of carbohydrate digestion occurs in the small intestine, where starch hydrolysis is completed (to glucose) and the disaccharides are hydrolyzed to their component monosaccharides. The enzymes responsible for these hydrolyses are produced in the pancreas and in the walls of the small intestine. All digestible carbohydrates at this stage are present as monosaccharides, in which condition they pass through the walls of the intestine, thence to the liver, which converts D-galactose and D-fructose to D-glucose. Ultimately, then, all digestible carbohydrates are converted into D-glucose.

The oxidation of carbohydrates is a source of energy for the body. The D-glucose produced by the digestive processes may be oxidized shortly after assimilation, or it may be stored for later use. It is conveyed by the blood to the tissues which require it. The usual content of glucose in the blood is 0.1%, but if it rises above or drops below this figure various mechanisms act to decrease or increase its supply. When the content is slightly less than 0.1% liver glycogen supplies glucose to the blood. At a still lower level body protein is converted into glucose. If the glucose content rises above 0.1%, as is likely after a meal, the glucose is removed to form liver glyco-



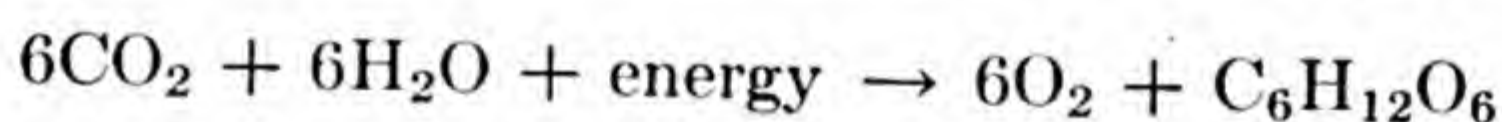
gen, muscle glycogen, or fat (at increasingly higher levels). At a still higher level (0.16%) glucose is excreted in the urine.

The functions of liver glycogen and muscle glycogen are somewhat different. The glycogen of the liver acts as a central store, since it may be converted into blood glucose which is removed by the tissues as required. The glycogen of the muscles, however, can only undergo oxidation. The liver is capable of converting either glucose or lactic acid into glycogen, but the muscles can use only glucose for this purpose. The conversion of glucose into glycogen is controlled by insulin, a hormone produced by the pancreas; the reverse reaction is influenced by epinephrine (adrenalin), a hormone produced by the adrenal glands.

Complete oxidation of the carbohydrates affords carbon dioxide and water, but if insufficient oxygen is available, as in vigorous exercise, lactic acid results. The acid accumulates in the muscles during exercise, but in periods of rest it travels in the blood to the liver where it is converted into glycogen. Lactic acid is a product of incomplete oxidation; that is, it is an intermediate in the complete oxidation to carbon dioxide and water.

The path of oxidation of carbohydrates is exceedingly complex and has been the subject of many investigations. Numerous carbohydrate esters of phosphoric acid are involved. Evidence has accumulated that a part of the energy made available by oxidation is used in making certain phosphoric acid derivatives, the hydrolysis of which provides an immediately available source of energy.

**Photosynthesis.** Plants are able to synthesize carbohydrates from carbon dioxide and water with the liberation of oxygen. The energy

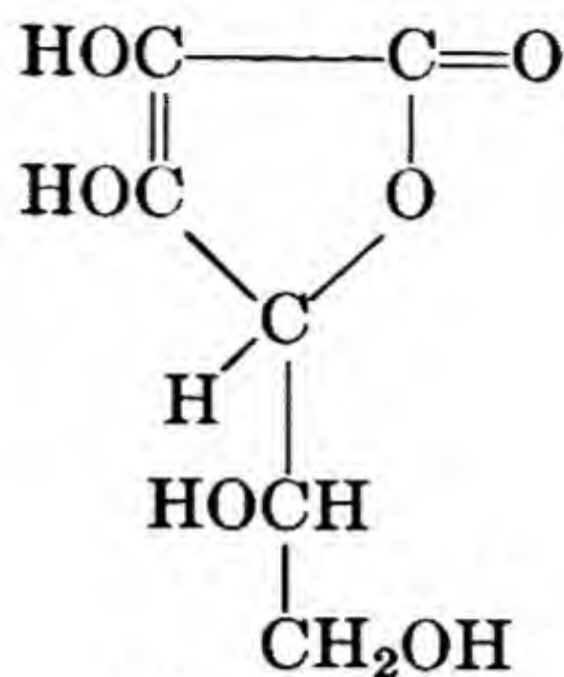


needed for this transformation is supplied by sunlight impinging on the leaves of the plants; hence the process is called photosynthesis. Chlorophyll, the green coloring matter in plants, is a component of the process, which is very complex and involves many intermediate compounds. Certain of these intermediates have been isolated, and parts of the photosynthetic process are well known.

## ▶ NATURALLY OCCURRING CARBOHYDRATE DERIVATIVES

**Vitamin C.** The most potent of a number of compounds with vitamin C activity is L-ascorbic acid. Scurvy, the deficiency disease



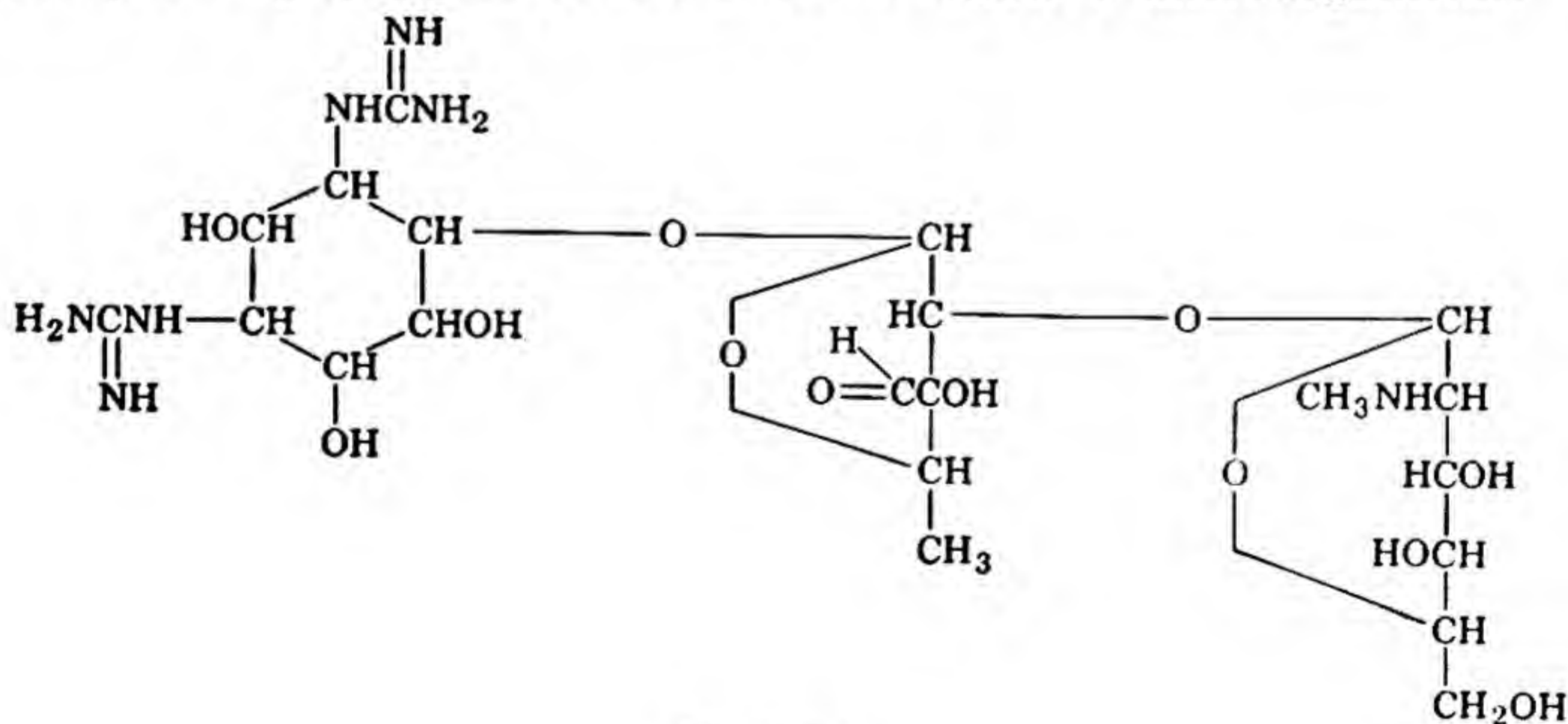


L-Ascorbic acid

associated with this vitamin, has been known for centuries. It was especially prevalent among seamen whose diets during long trips at sea were deficient in fresh fruits and vegetables. As early as 1795 ships of the British navy were required to carry fresh limes (which contain vitamin C) to prevent outbreaks of scurvy. As a consequence, British sailors became known as "Limeys." Scurvy is more likely to occur when peoples become isolated from commerce so that their diet becomes restricted. War nearly always brings outbreaks of scurvy with it. The symptoms of scurvy include hemorrhages, swelling, and redness, especially of the gums, pains in the joints, and abnormalities of the connective tissue. The biochemical function of L-ascorbic acid is unknown, but comparatively large amounts of it are required by man.

L-Ascorbic acid is widely present in foods, but cooking or even long exposure to the open air destroys some of the vitamin. The best sources are citrus fruits, tomatoes, green peppers, and parsley. Other vegetables also have appreciable amounts of the vitamin but lose much of it in cooking.

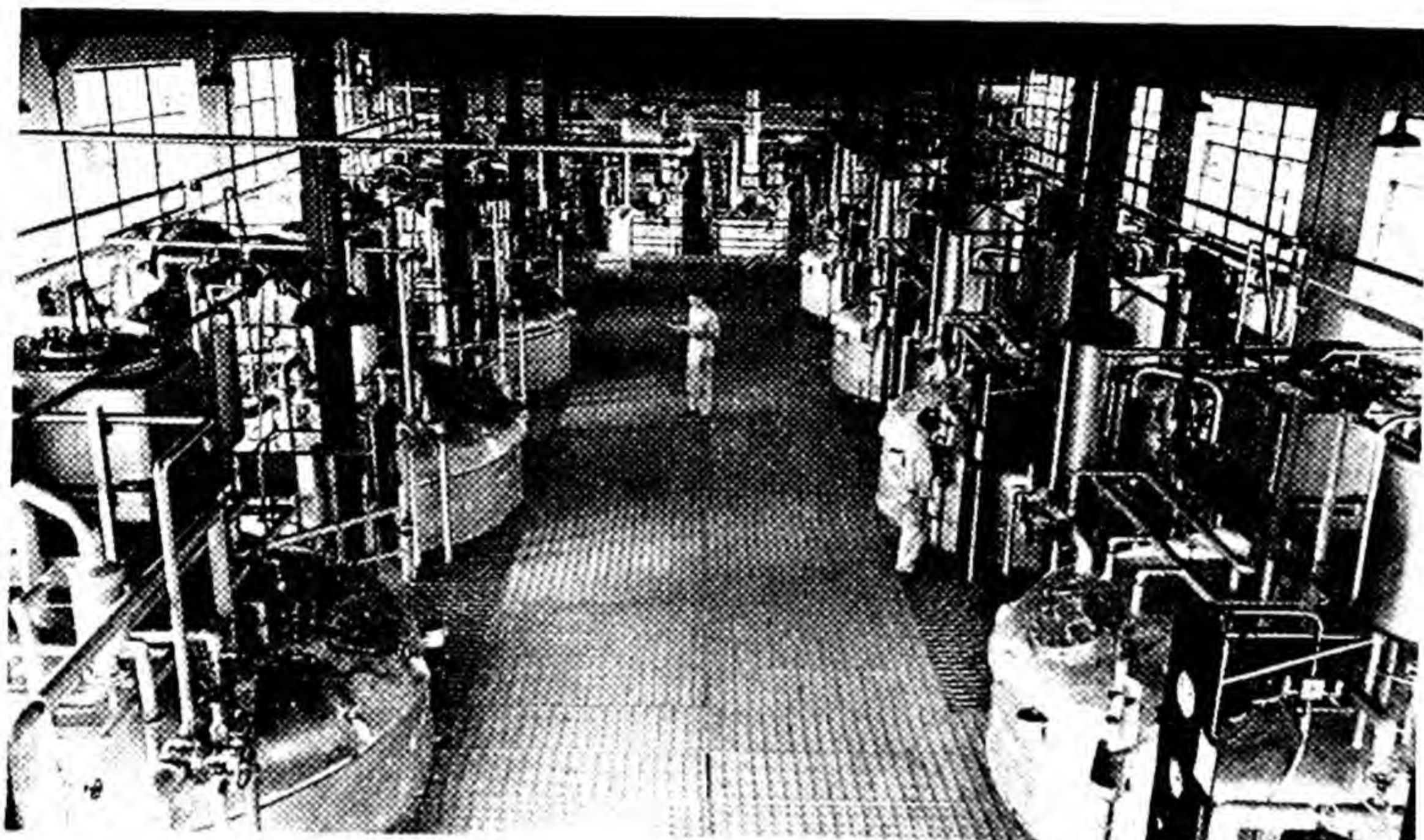
✧ **Carbohydrate Antibiotics.** Streptomycin, in contrast to the penicillins, is largely effective with Gram-negative microorganisms. It



Streptomycin

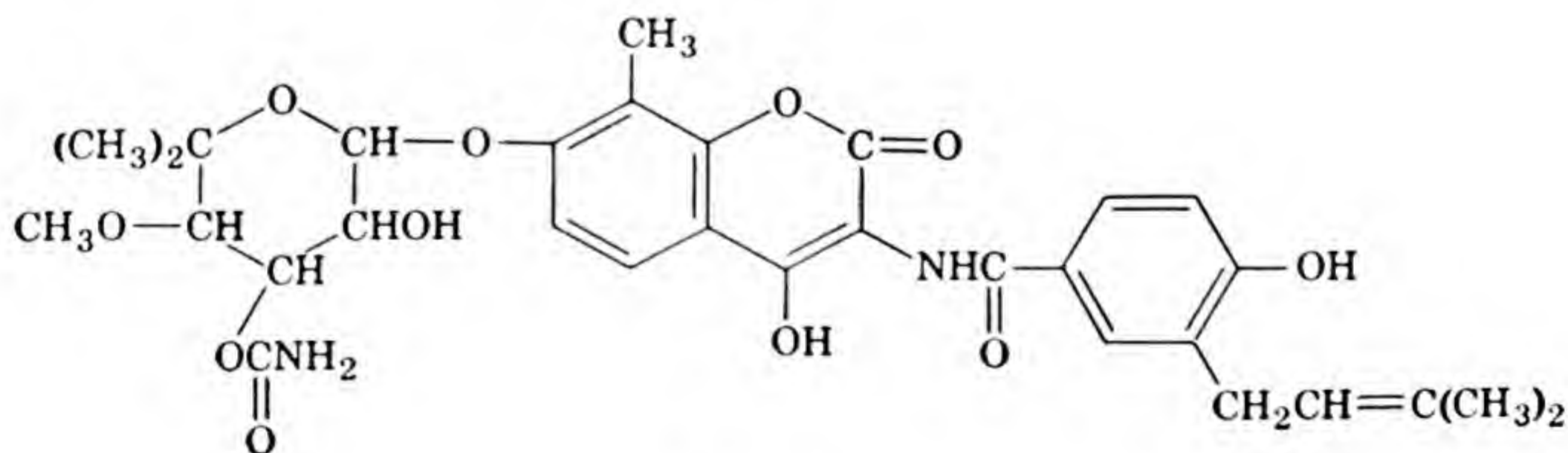


is produced by the soil organism *Streptomyces griseus* and some related organisms. Dihydrostreptomycin, in which the aldehyde has been reduced to a primary alcohol, is more frequently used because the undesirable effects upon the inner ear, sometimes occurring with streptomycin, are less frequently met. It is employed in some cases of tuberculosis, tularemia, brucellosis, meningitis, various urinary tract infections, wounds, and preoperatively in abdominal surgery.

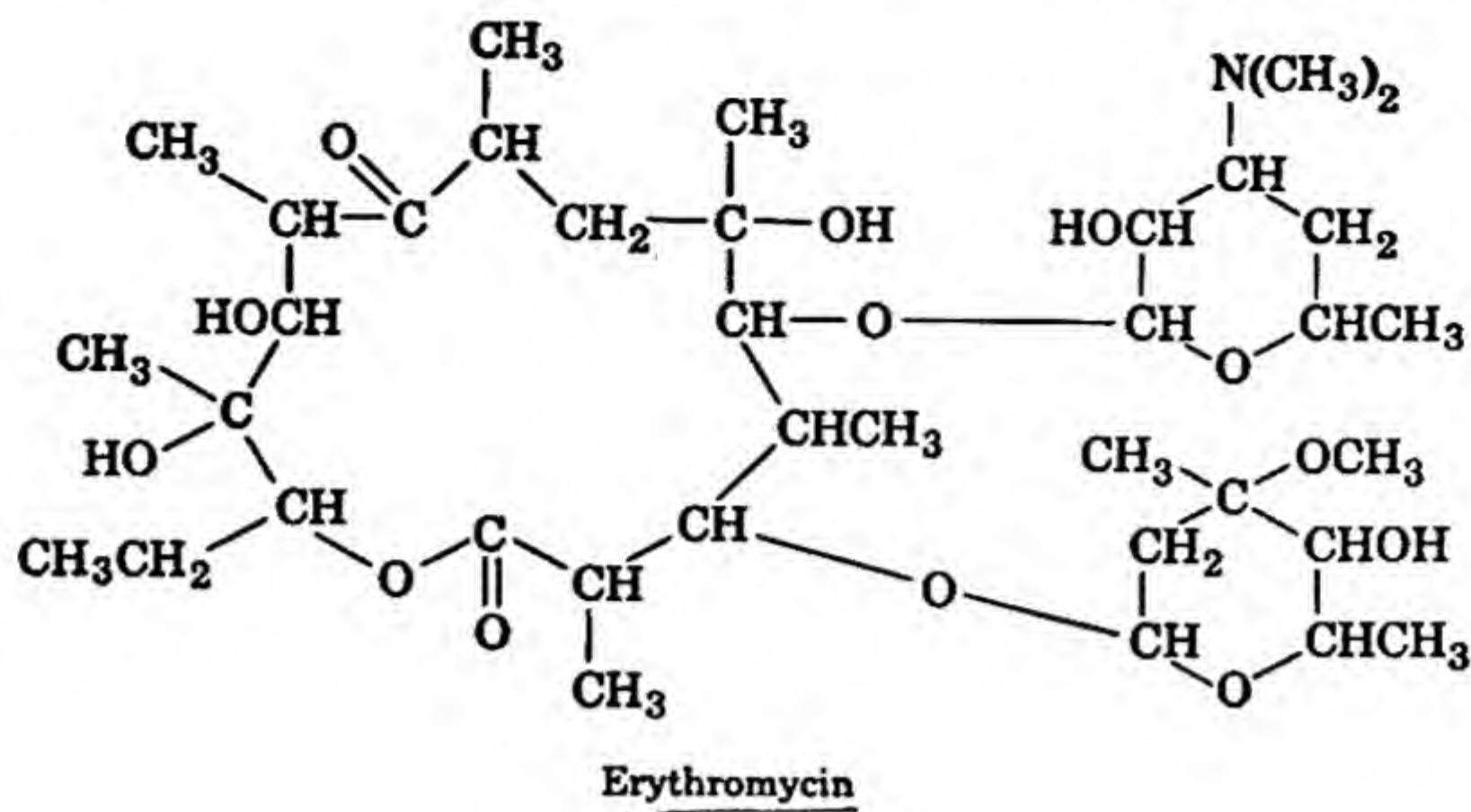


Fermentation tanks used in the manufacture of streptomycin. The antibiotic is a product of the metabolism of the microorganism, *Streptomyces griseus*. Only the top portion of the tanks can be seen—the whole tank extends downward to a lower level. (Photograph courtesy of Merck and Company.)

Other examples of antibiotics that contain carbohydrate groups are puromycin (Chapter 19), kanamycin, novobiocin, erythromycin, and a number of others related to it.



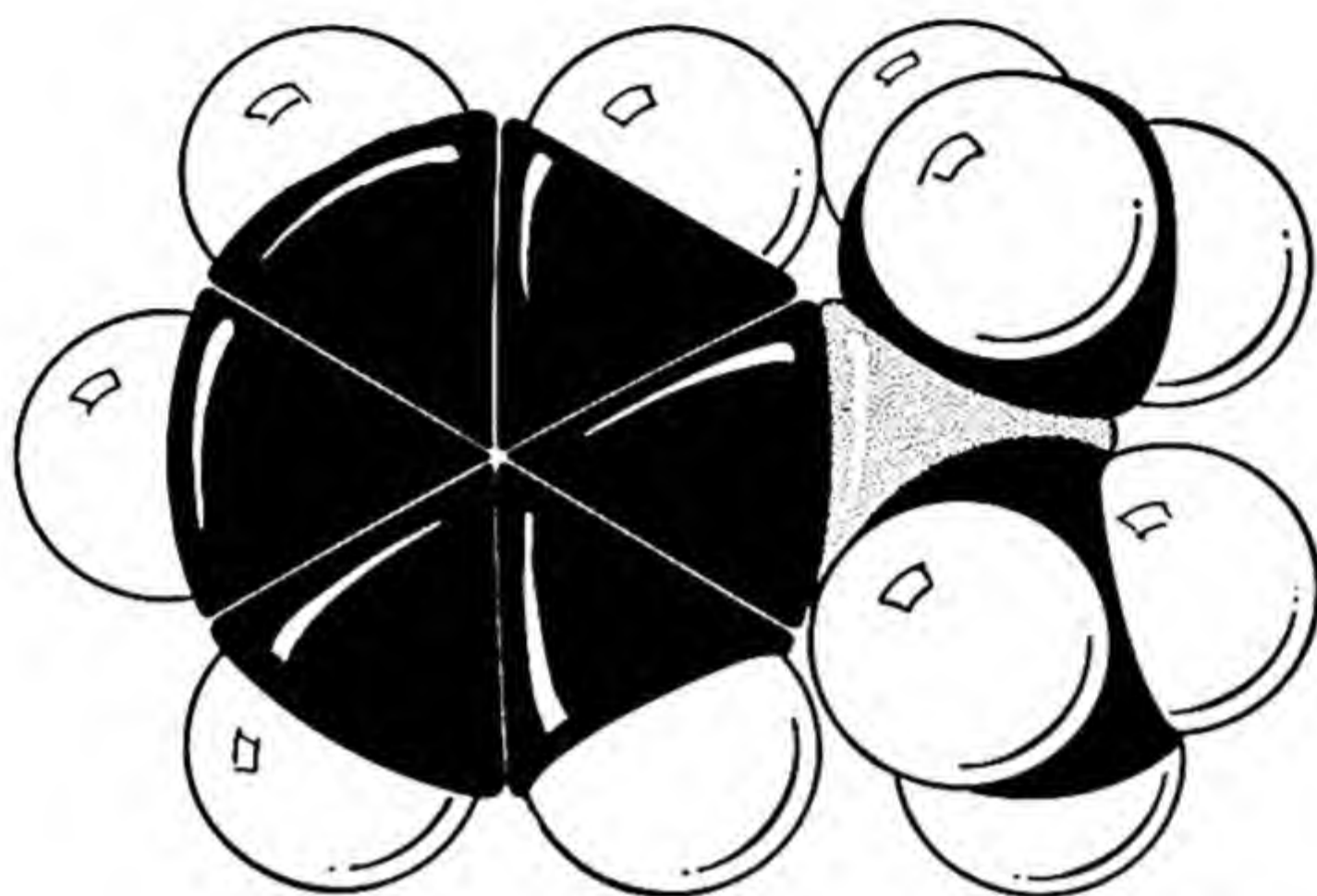
Novobiocin



## ► QUESTIONS

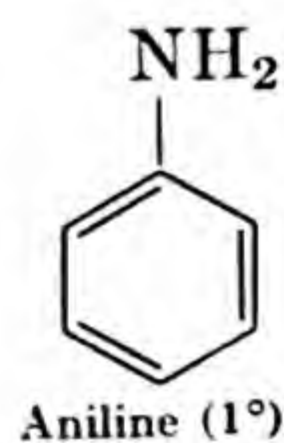
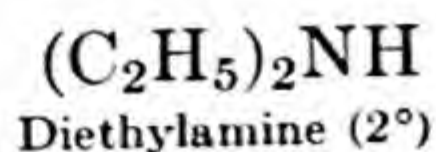
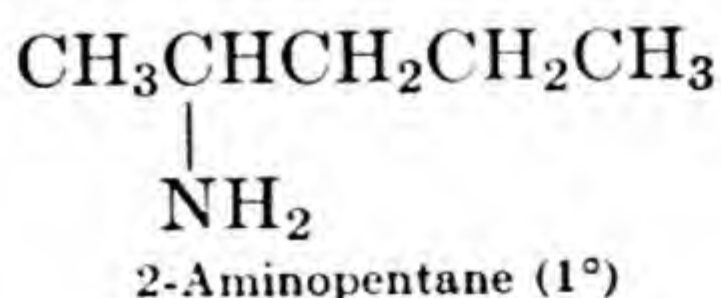
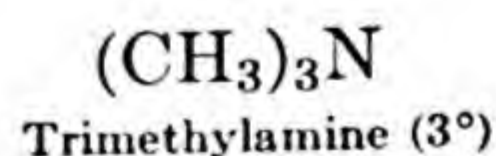
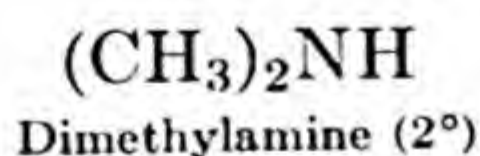
1. Write the configurational formulas of all the aldopentoses and show which are enantiomorphs.
2. Write a possible structural formula for raffinose.
3. Write the formula of an aldohexose which would give the same osazone as D-galactose.
4. Show formulas for a fructosan, a ketopentose, and L-glucose.
5. When sucrose is heated with phenylhydrazine no precipitate forms at first, but later D-glucosazone is produced. Explain these phenomena.
6. Could a monosaccharide be a nonreducing sugar? Explain.

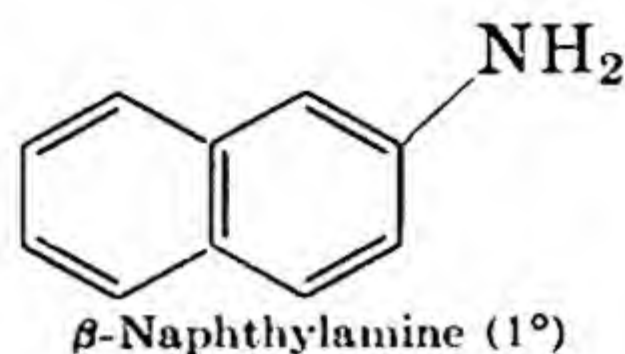
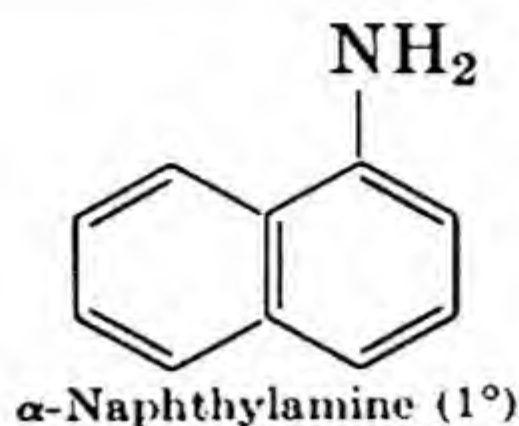
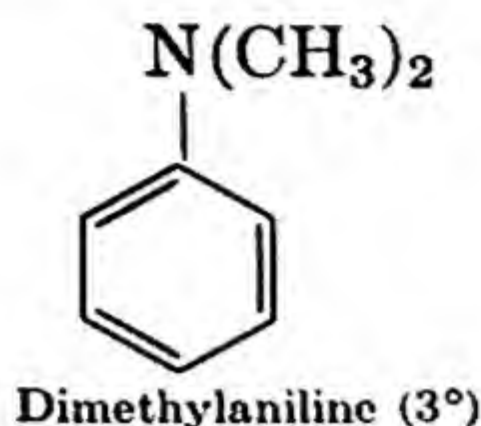




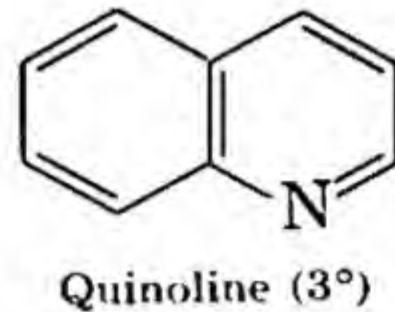
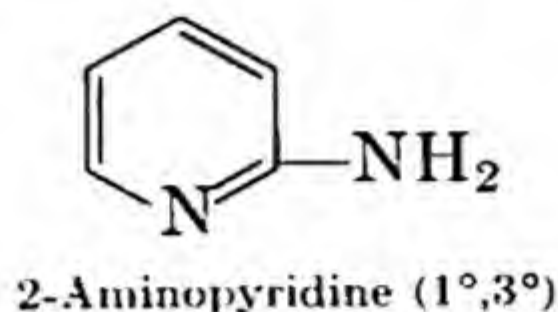
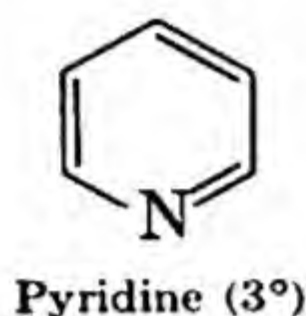
The model represents dimethylaniline, an aromatic tertiary amine, important in the dye industry. The benzene ring with its attendant hydrogen atoms and the nitrogen atom are essentially coplanar.

The amines are the organic bases. They may be regarded as derivatives of ammonia, in which hydrogen atoms have been replaced by alkyl, aryl, or heteryl radicals, and are classified as primary, secondary, or tertiary, depending upon the number of hydrogen atoms which have been replaced. When one or more of the groups attached to the nitrogen atom is aromatic the compound is said to be an aromatic amine. Examples of amines and their classes are noted here.

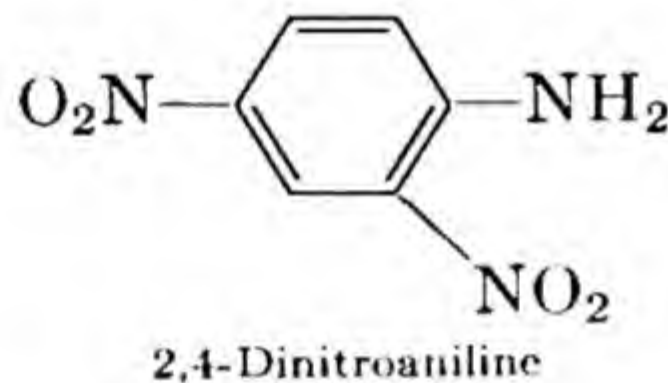
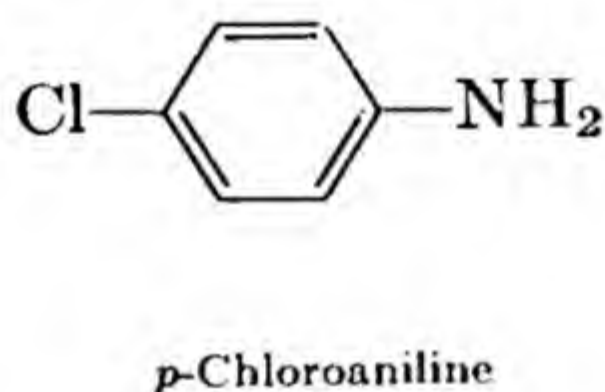




In heterocyclic compounds the nitrogen atom may be part of a ring.

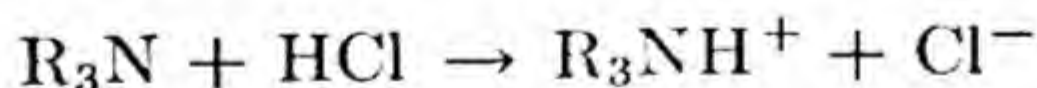
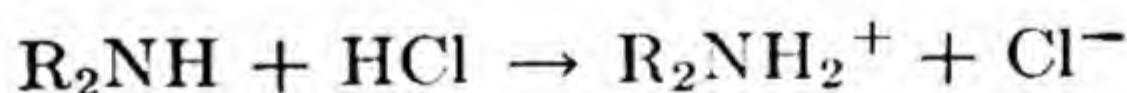


The nomenclature of the amines is partly revealed by these examples. Amines having purely aliphatic groups are most often named by specifying the groups attached to the nitrogen atom and appending the suffix "amine." Many aromatic amines are named by reference to the simplest example, aniline.



Heterocyclic amines have trivial names or are considered as derivatives of the fundamental heterocyclic rings (see Chapter 19).

Amines, like ammonia, are basic and form salts with acids.



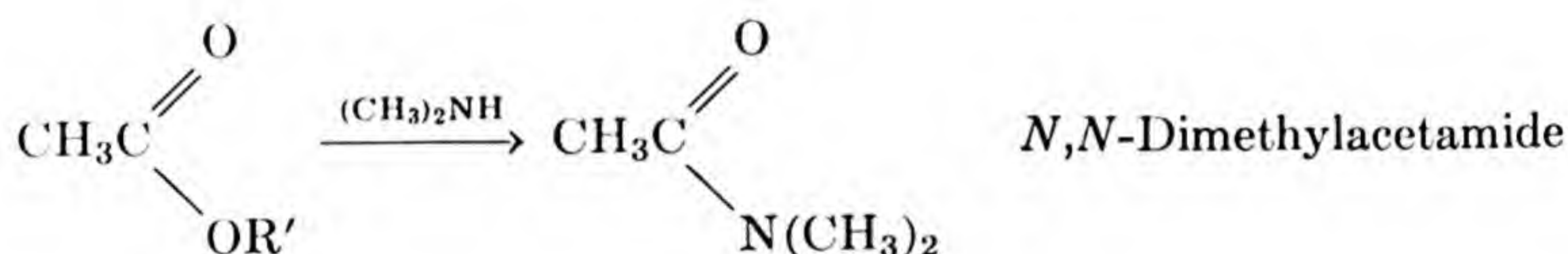
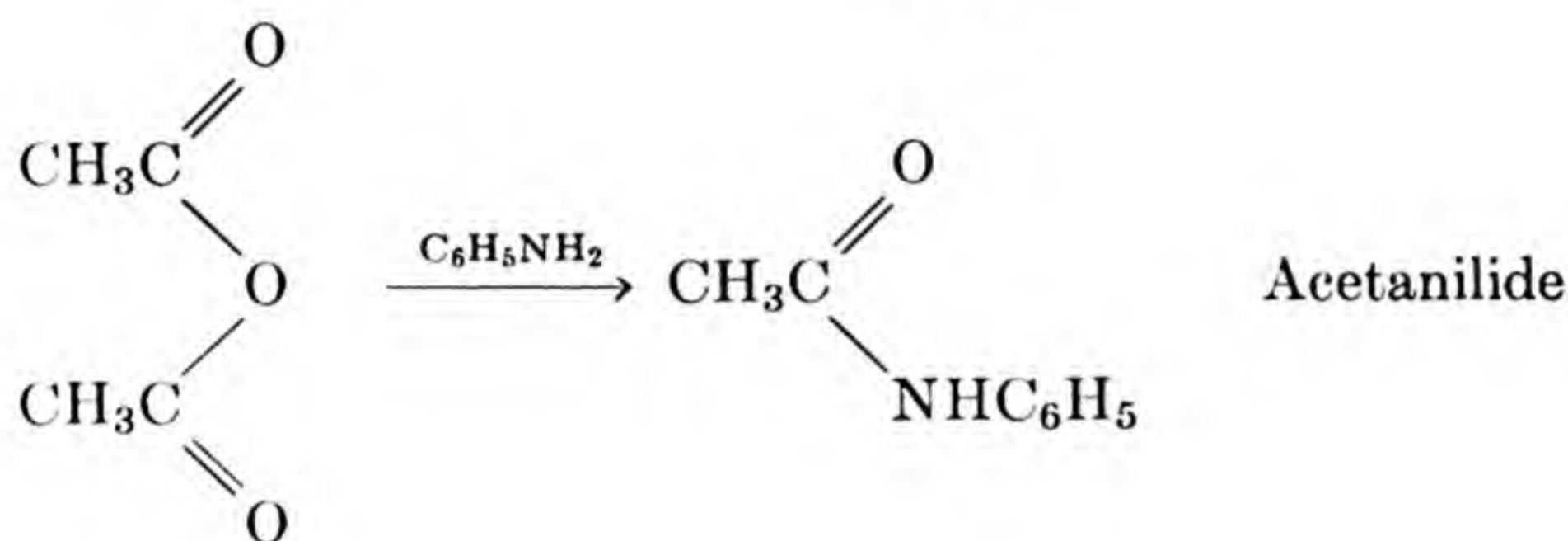
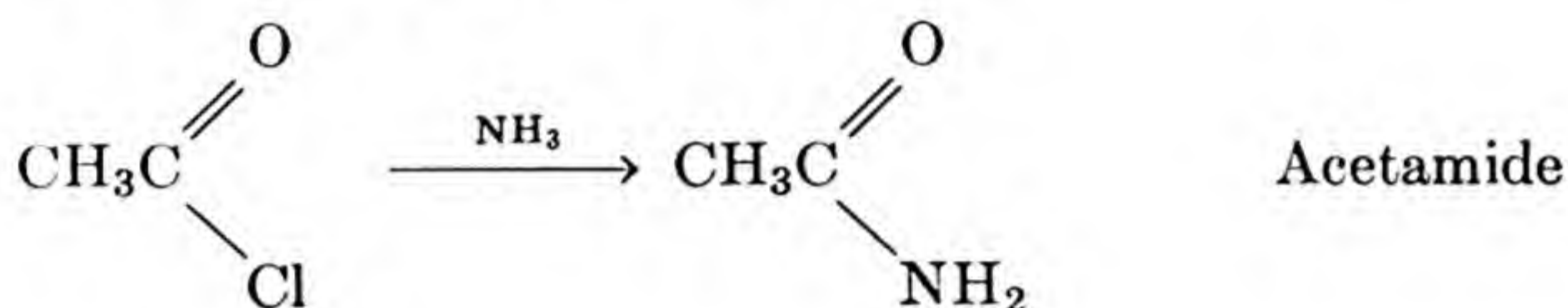
The salts may be considered to be substituted ammonium salts, just as the amines are substituted ammonias. The salts are nearly always soluble in water, so that amines which are insoluble in water are dissolved by aqueous acids, such as hydrochloric or sulfuric acid. Aromatic amines are less basic than their aliphatic counterparts. This diminution in the basicity of the amino group is due to the influence of the aryl group; if two or three aryl groups are present, the amine is almost neutral. Thus diphenylamine shows little tendency to form



salts. It will be remembered that acid radicals have this same effect,

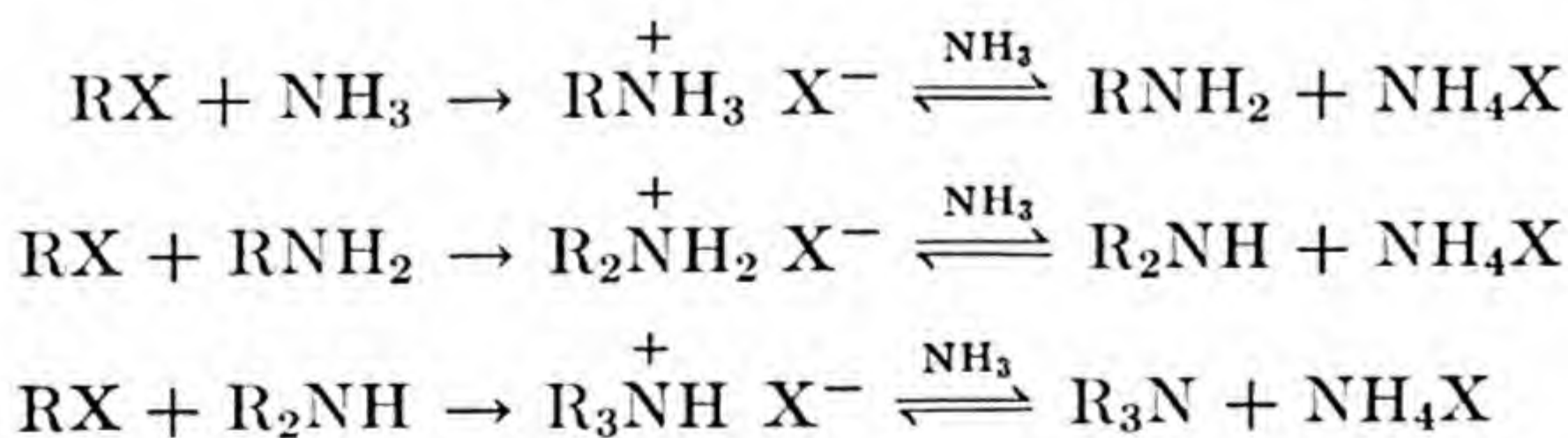
for amides  $\left( \begin{array}{c} \text{O} \\ \parallel \\ \text{RC} \\ \backslash \\ \text{NH}_2 \end{array} \right)$  are neutral compounds.

The parallel between ammonia and amines extends to many reactions, as, for example, the formation of amides by the reaction with acid chlorides, anhydrides, or esters.



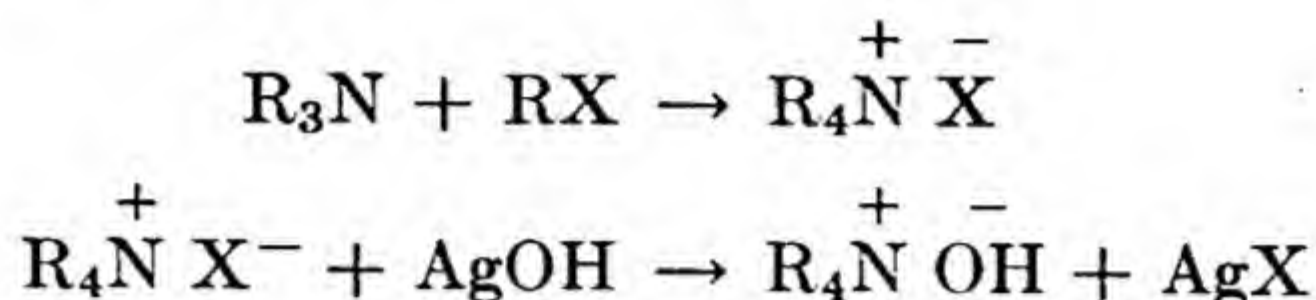
## ► THE PREPARATION OF AMINES

Aliphatic amines can be made by treating alkyl halides with ammonia. This method has the disadvantage that it gives a mixture

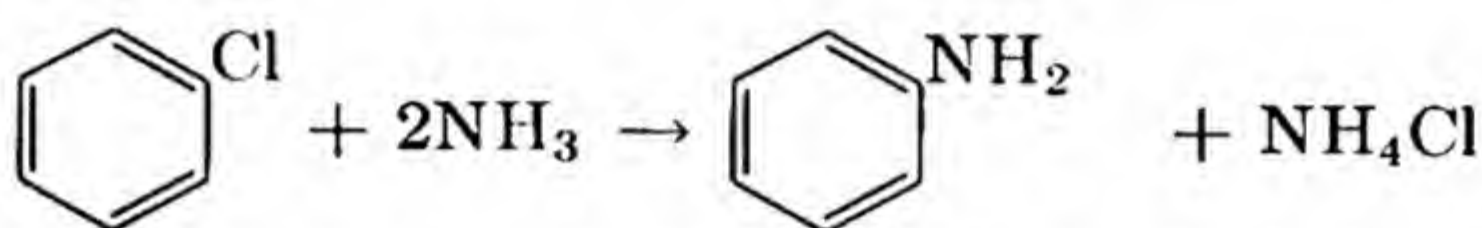


of primary, secondary, and tertiary amines, which may be difficult to separate. A fourth product is formed by the reaction of the tertiary amine with the alkyl halide. It has four alkyl groups attached

to the nitrogen atom and as a consequence is called a quaternary ammonium salt. The corresponding bases may be formed by treatment of the quaternary halide with silver hydroxide. These hydroxides are very strong bases comparable to sodium or potassium hydroxide. Most of them, however, are not very stable.

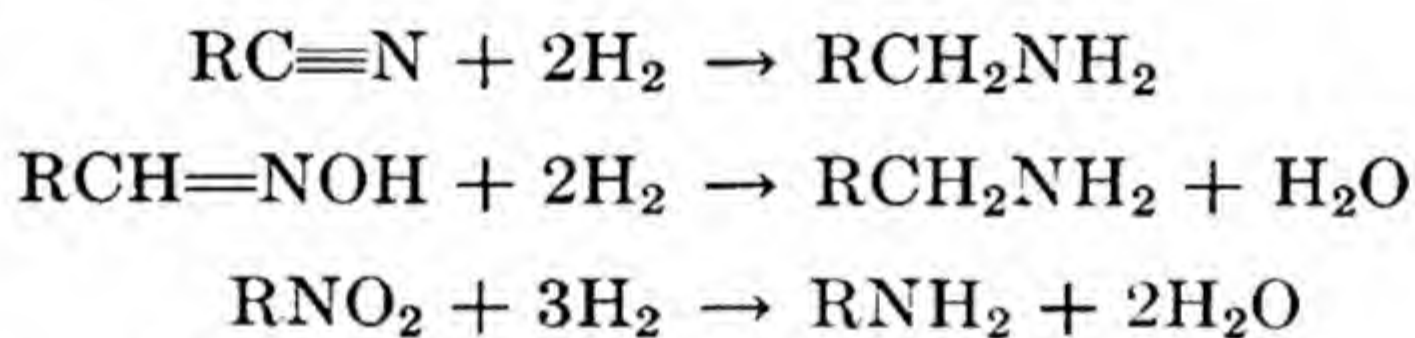


Aromatic halogen derivatives react with ammonia to form primary amines, but more vigorous conditions are usually required. Thus the conversion of chlorobenzene to aniline by ammonia requires high temperature and pressure.



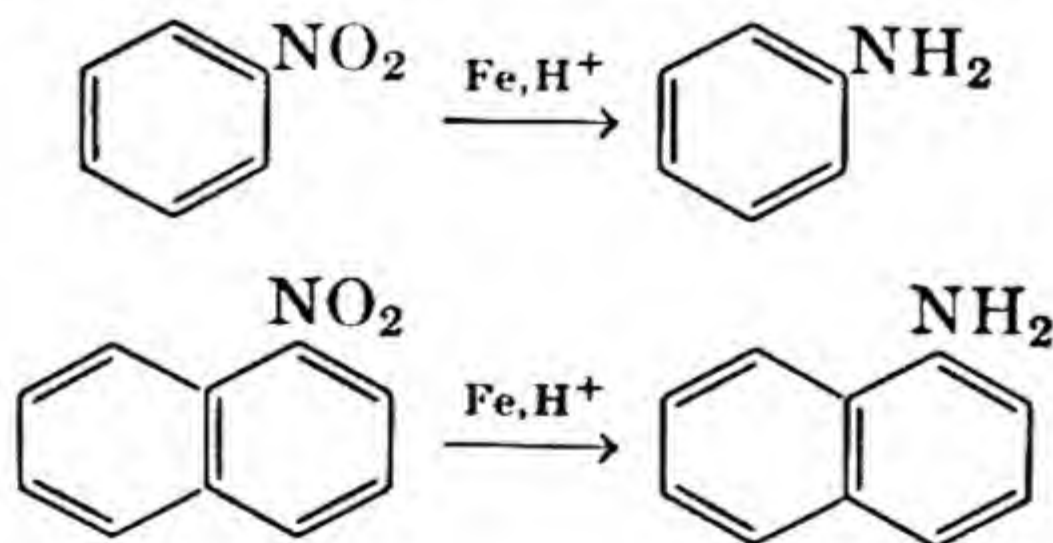
The presence of nitro groups *ortho* or *para* to the halogen atom renders conversion to the amine easier.

Primary amines can also be made by the reduction of nitriles, oximes, or nitro compounds.



Nitro compounds are the most frequently employed and are particularly important in the preparation of aromatic amines. The reduction may be performed catalytically, but metal-acid combinations, such as iron and sulfuric acid or tin and hydrochloric acid, are commonly used. With such chemical methods, the amine is actually produced as a salt from which the free base can be obtained by treatment with sodium hydroxide.

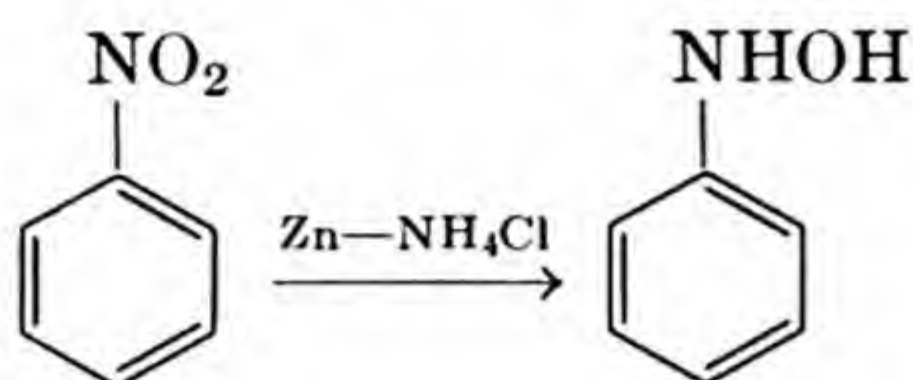
Such aromatic amines as aniline and 1-naphthylamine are manufactured by the reduction of the corresponding nitro compounds.



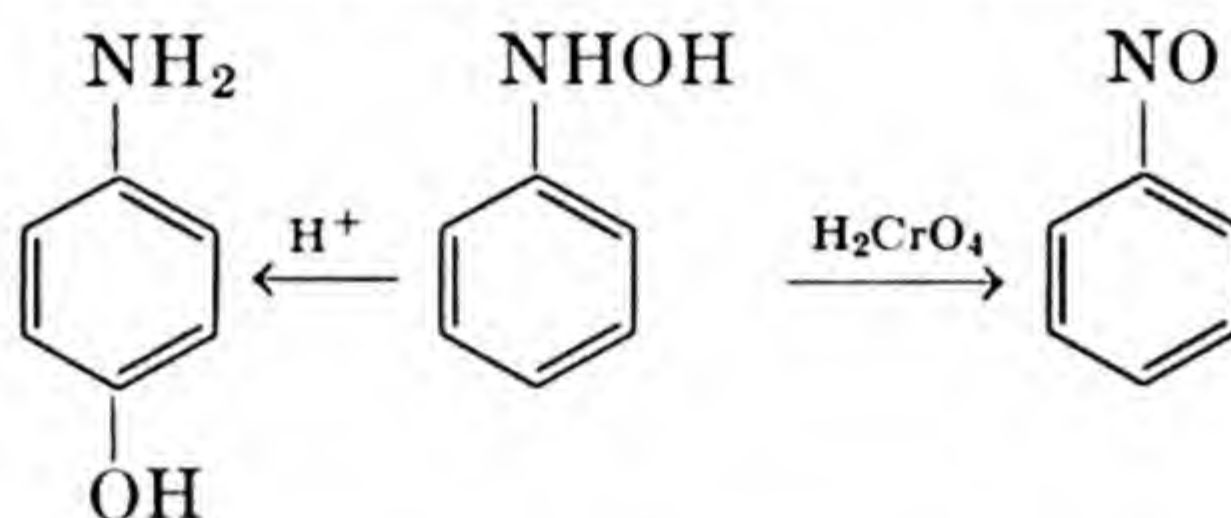


**Other Reduction Products of Aromatic Nitro Compounds.**

When reducing agents other than metal-acid combinations are used aromatic nitro compounds may yield substances other than amines. Thus the reduction of nitrobenzene with zinc and ammonium chloride yields phenylhydroxylamine.

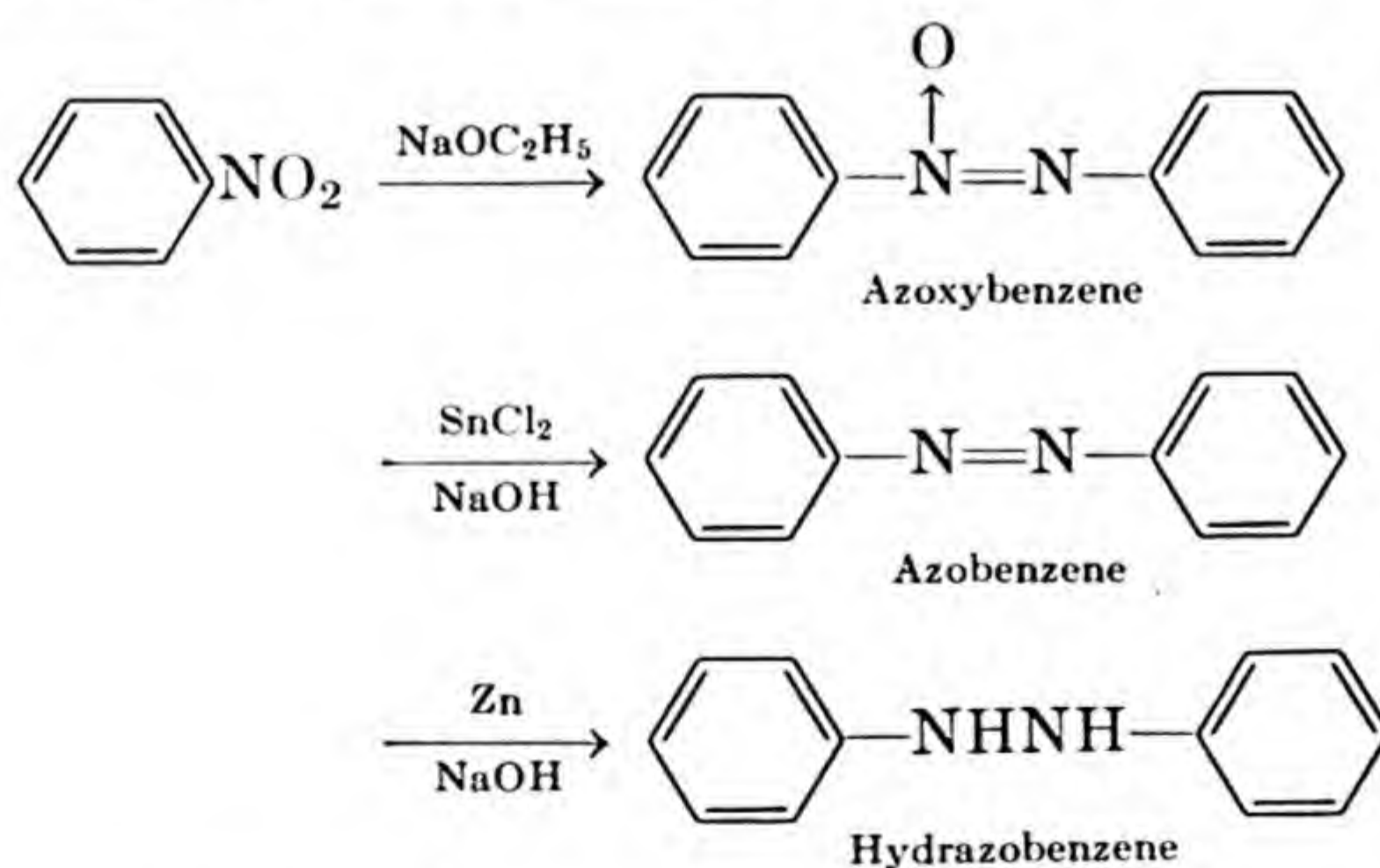


Phenylhydroxylamine is of interest because it can be oxidized to nitrosobenzene and because treatment with strong acids produces *p*-aminophenol, a useful photographic developer.



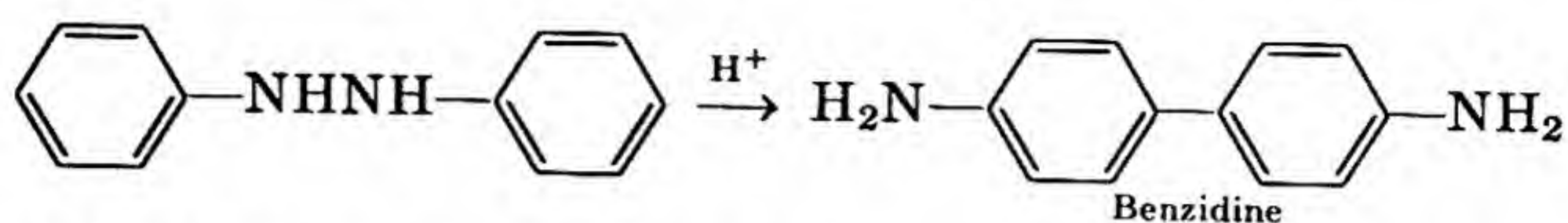
The production of *p*-aminophenol is an example of a class of reactions, known as rearrangements, which are characterized by the interchange of groups within a molecule.

In alkaline solution the reduction of nitrobenzene is accompanied by coupling, and for this reason it is said to be a bimolecular reduction. Several products are possible.

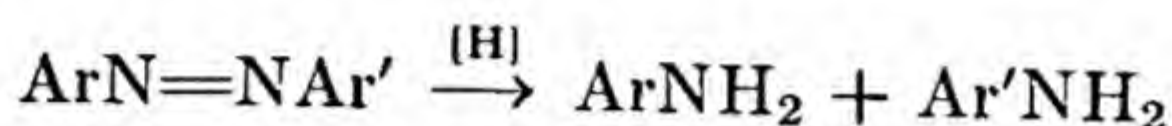


Azobenzene is the simplest of the aromatic azo compounds, a group which includes many dyestuffs. Hydrazobenzene is industrially important because of the rearrangement which occurs when it is treated

with strong acids. The reaction is known as the *benzidine rearrangement*. Benzidine is an important dye intermediate.

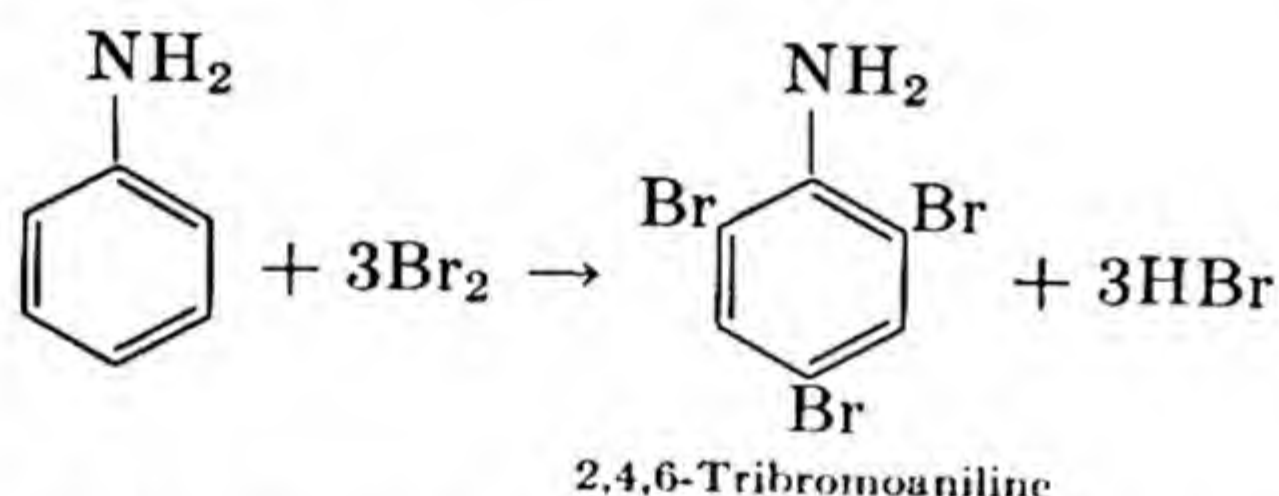


All of the bimolecular reduction products, on treatment with a metal-acid combination, yield two primary amine molecules. This reaction constitutes the best method of preparation for some amines.

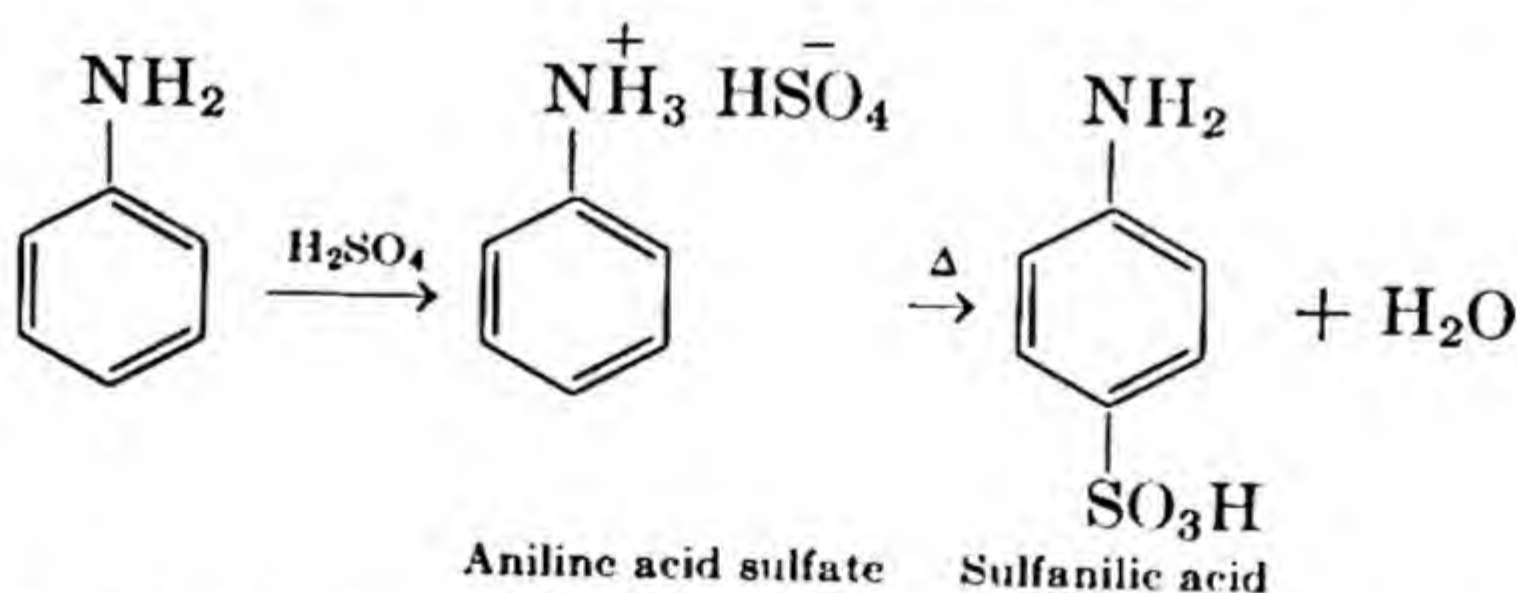


### ► THE REACTIONS OF AROMATIC AMINES

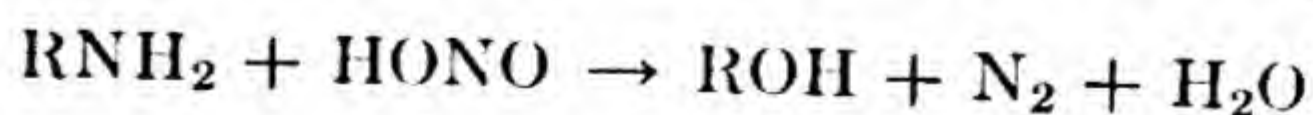
The presence of an amino group on the benzene ring renders it very reactive toward substitution. When aniline is brominated, for example, it is difficult to stop the substitution before three bromine atoms are introduced.



Attempts to sulfonate aniline with sulfuric acid yield a salt, which, upon heating, undergoes rearrangement to yield sulfanilic acid.

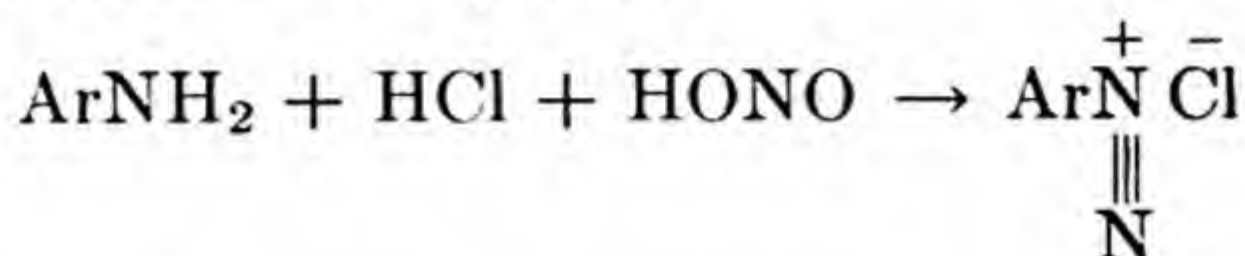


**Reaction with Nitrous Acid.** The reaction of amines with nitrous acid has been found to be a useful method of distinguishing the classes. A solution of the amine in an acid, often hydrochloric acid, is treated at 0–5° with sodium nitrite. Primary aliphatic amines

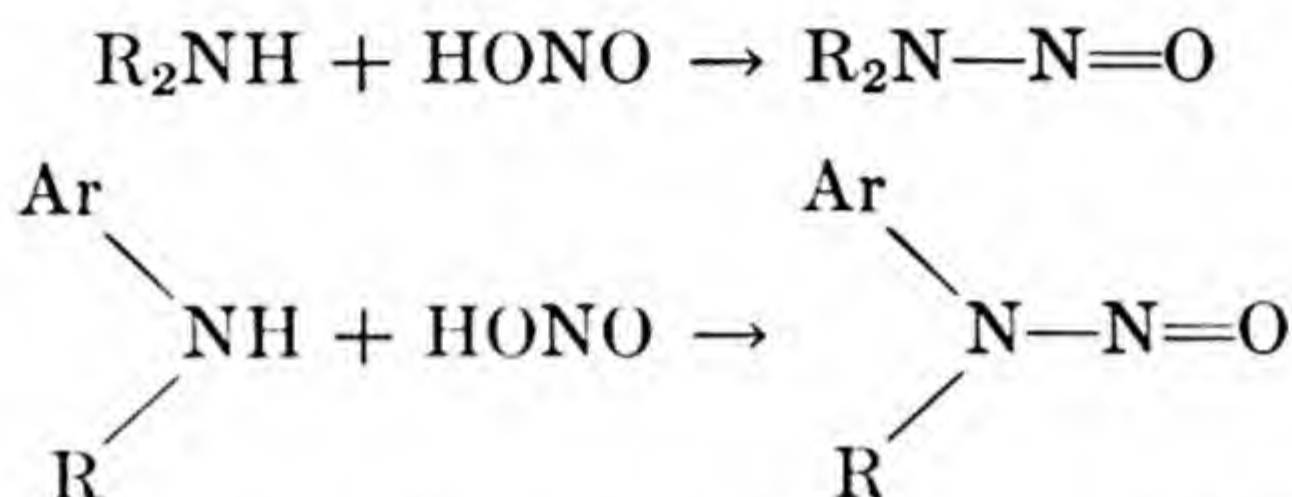




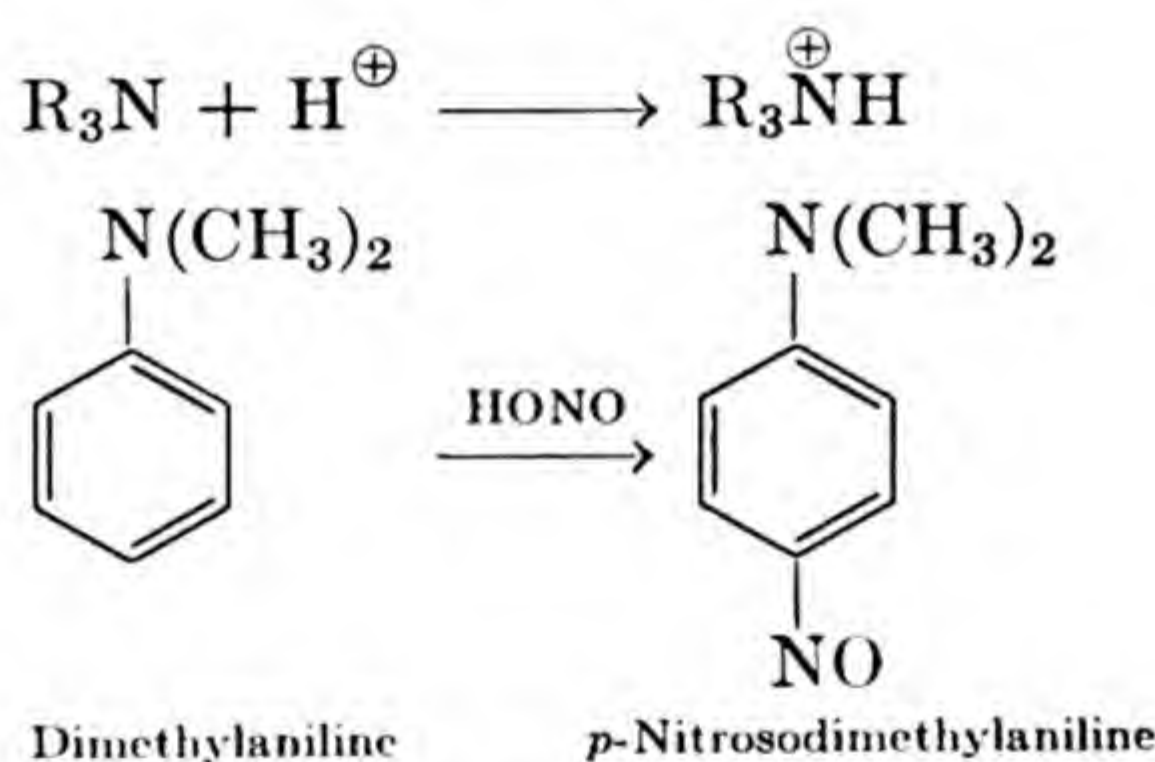
give nitrogen. Primary aromatic amines undergo diazotization, the occurrence of which is detected by the production of a red color if the solution is treated with a phenol.



Secondary amines, whether aliphatic or aromatic, form nitrosoamines, oily liquids usually yellow or orange.



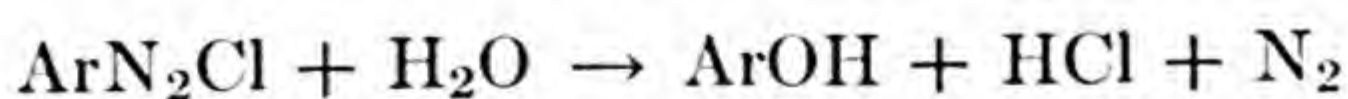
Tertiary aliphatic amines do not undergo any visible change. The amines are, of course, converted into salts. Tertiary aromatic amines usually undergo nitrosation, though other reactions may occur. The nitroso compounds may be yellow to green, and the test may therefore be confusing.



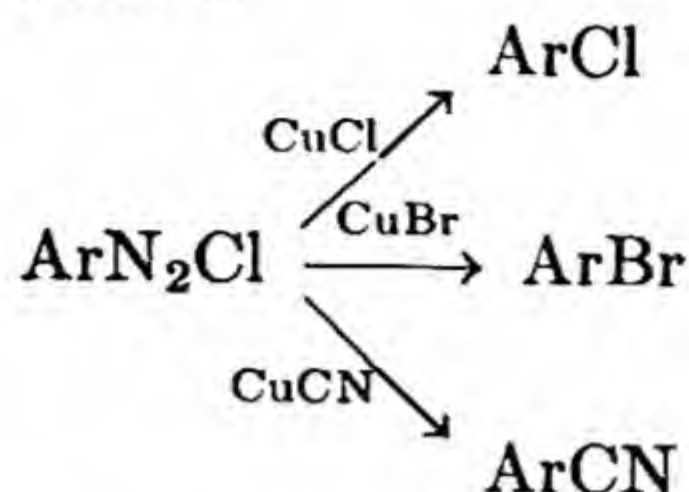
**Diazonium Solutions.** The diazotization previously mentioned is of great importance. The diazonium solutions produced by it are very reactive. They can undergo three general types of reaction: reduction, replacement, and coupling. Reduction with stannous chloride or sodium sulfite provides a source of hydrazine derivatives.



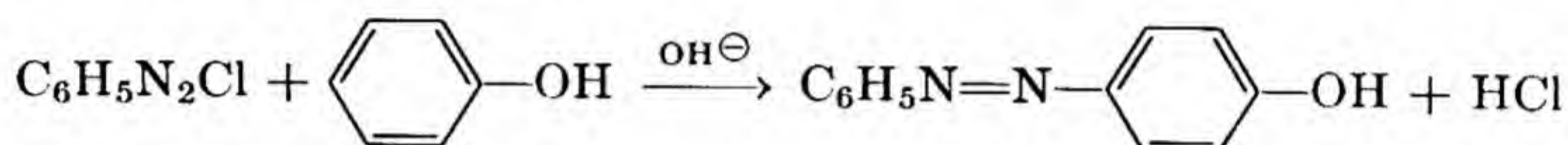
Replacement reactions of diazonium compounds permit the preparation of a variety of aromatic substances. Nitrogen gas is always evolved. For example, if a diazonium salt solution is warmed, a hydroxyl group enters the aromatic ring.



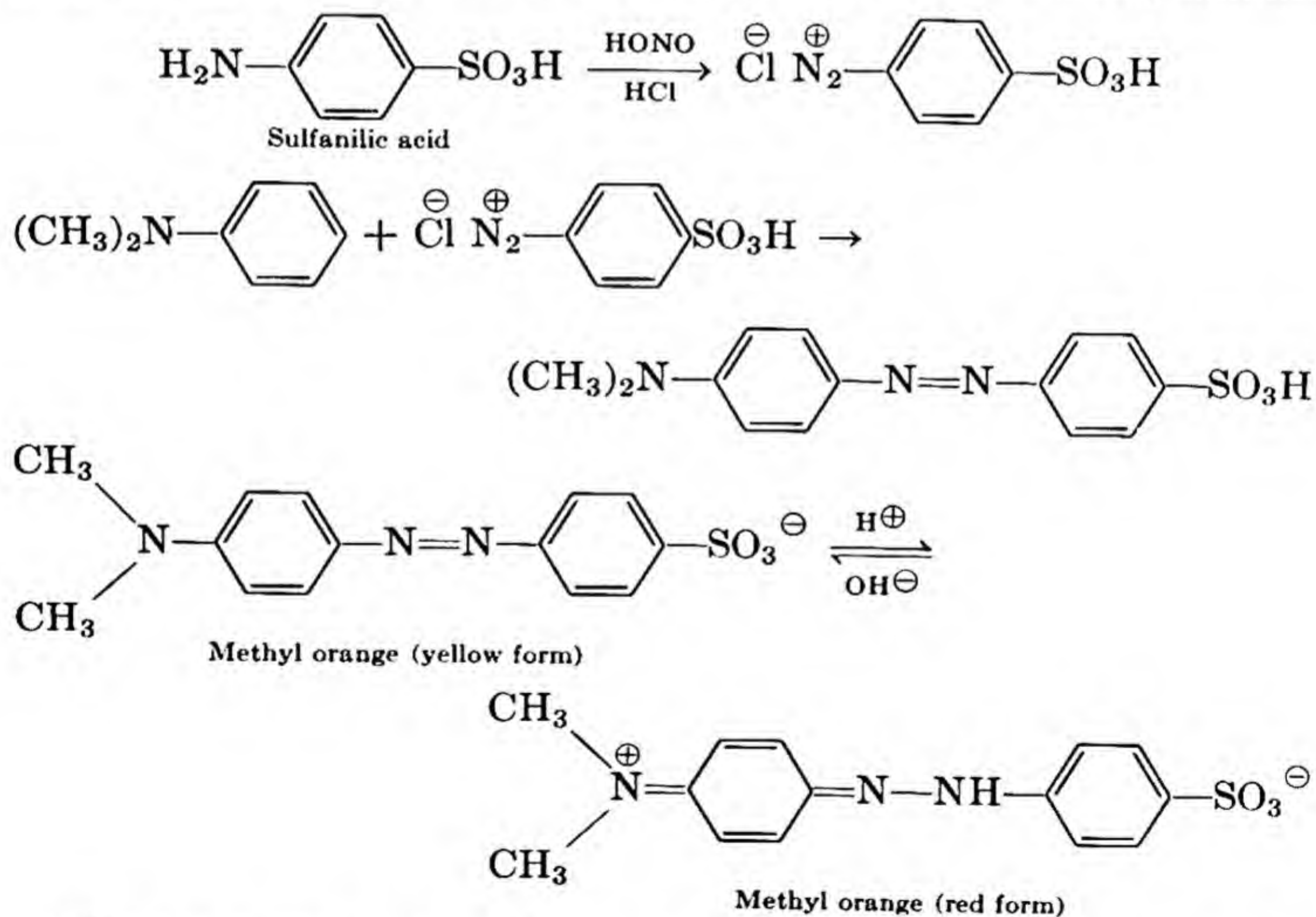
In the presence of the appropriate cuprous salt, a halogen atom or a cyano group can be introduced.



**Azo dyes.** If a phenol or aromatic amine is added to a diazonium solution, coupling takes place and an azo compound is formed. For example, benzenediazonium chloride couples with phenol as shown in the following equation.



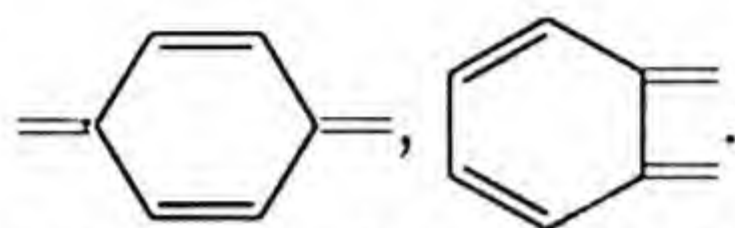
The  $-\text{N}=\text{N}-$  group in compounds of this type is called the *azo* group. Compounds containing this group, *i.e.*, azo compounds, are colored. Many commercial dyes and acid-base indicators contain the azo group. Methyl orange is an acid-base indicator which is prepared by coupling diazotized sulfanilic acid with dimethylaniline.



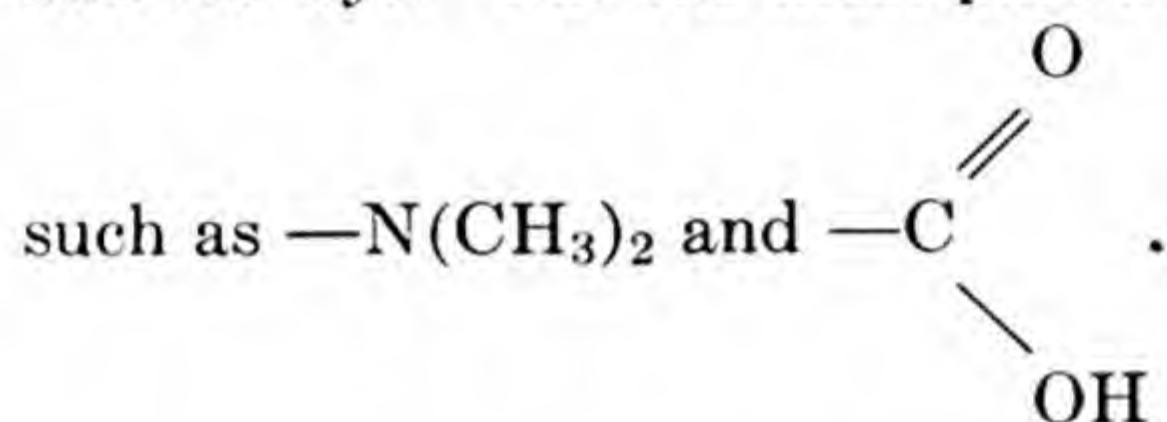
The azo group is one of several that give color to compounds in which they occur. These groups are called chromophores, and any



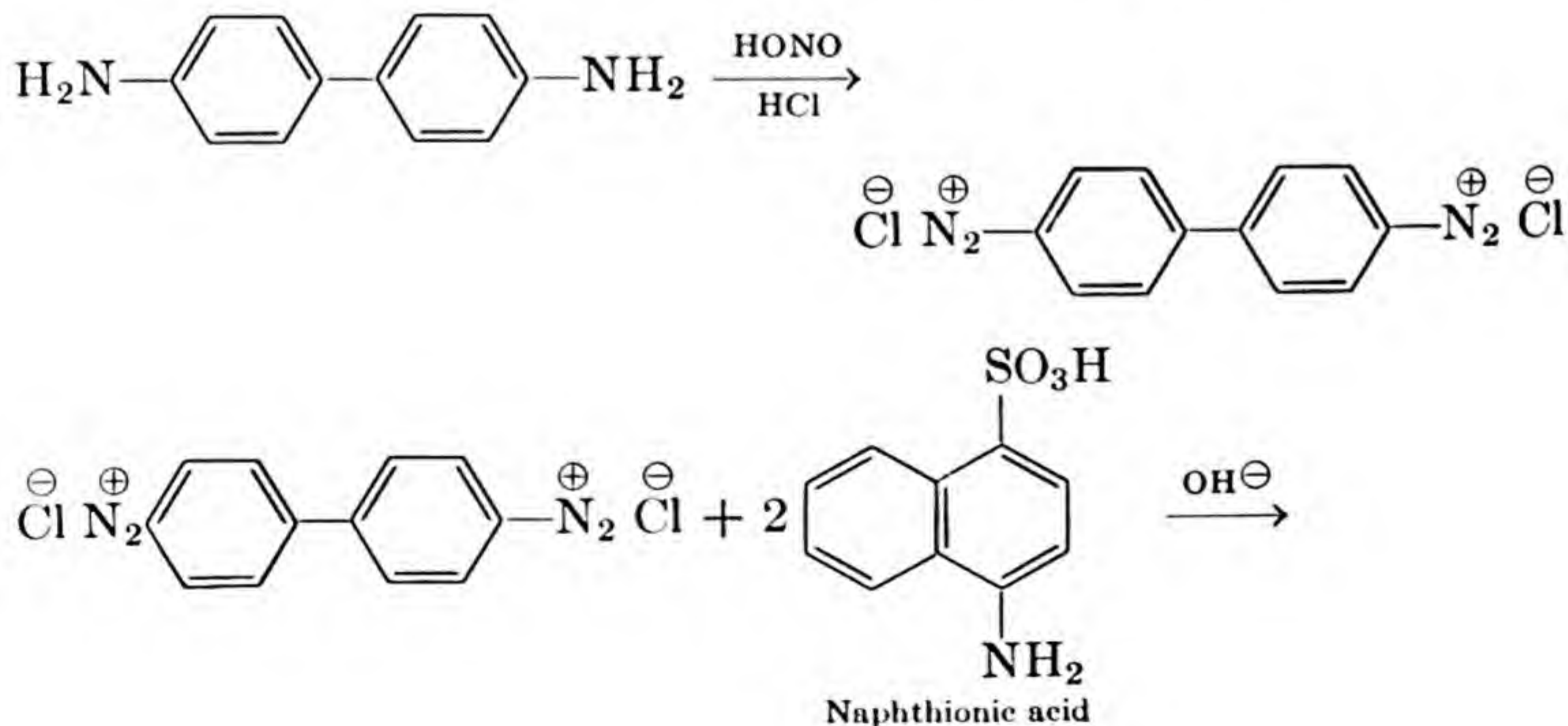
compound containing such a group is colored. Inspection of the structural formula of a compound therefore enables us to predict whether it is colored. Other chromophoric groups are  $\text{—C(=O)—C(=O)—}$ ,  $\text{—NO}_2$ ,  $\text{—NO}$ ,

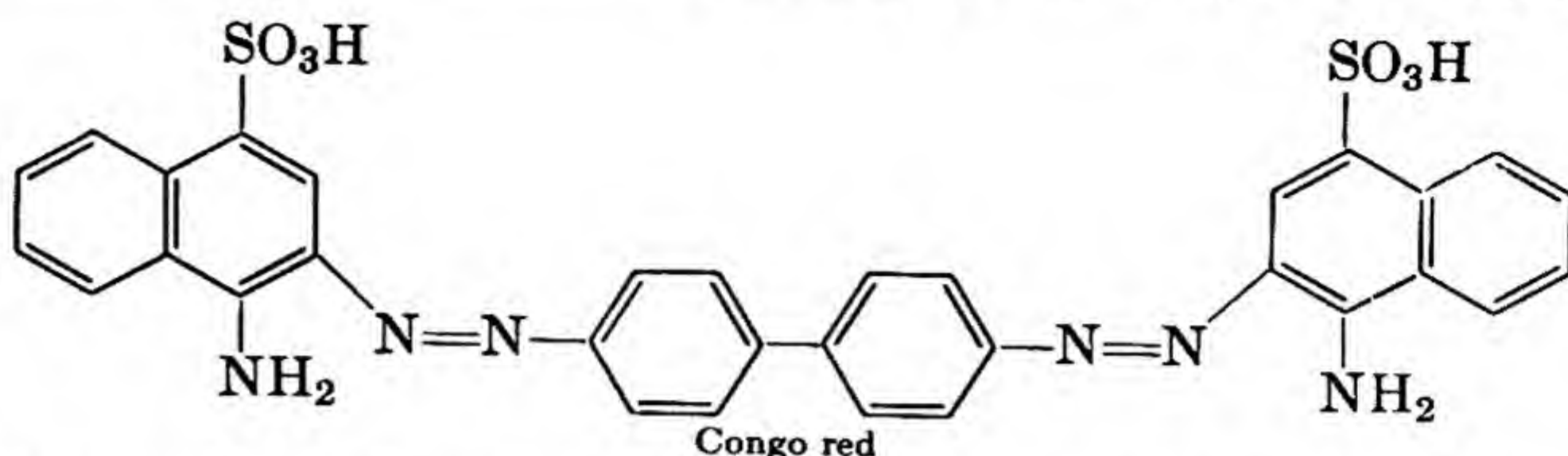


Not all colored compounds, however, are satisfactory dyes. In addition to color, dyes must have other properties, such as fastness to light and laundering, and they must be held by the fabric. For this latter requirement dyes often contain *auxochrome* groups. These groups are especially important in dyeing wool or silk, in which there is a chemical reaction between the fabric and the dye. For the most part auxochromes are salt-forming groups

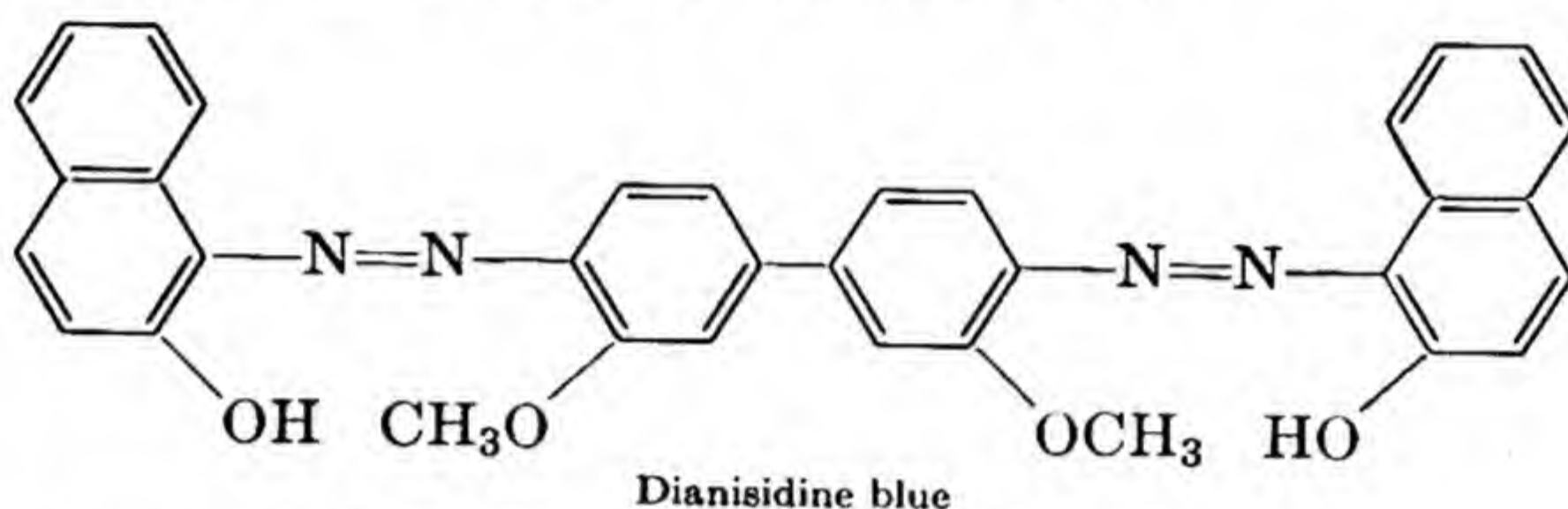


Dyes can be classified either by reference to their chemical structure (e.g., azo dyes) or by the method used in their application. Direct dyes are those which will dye cloth if it is heated in the solution, rinsed, and dried. Many dyes are direct for protein materials, such as wool and silk, but few are direct for cotton. Direct dyes contain acidic or basic groups and are classed as acid or basic dyes, accordingly. Congo red is one of the simplest examples of a class of azo dyes which for some unknown reason are direct for cotton. Most of the dyes sold for household use are of this type. They are obtained by diazotization of both of the amino groups of benzidine, followed by coupling with an aromatic amine or phenol.





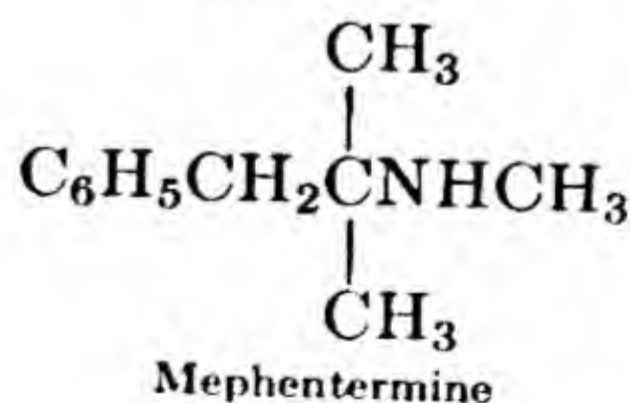
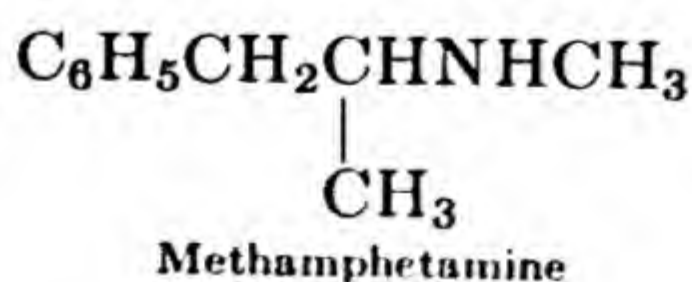
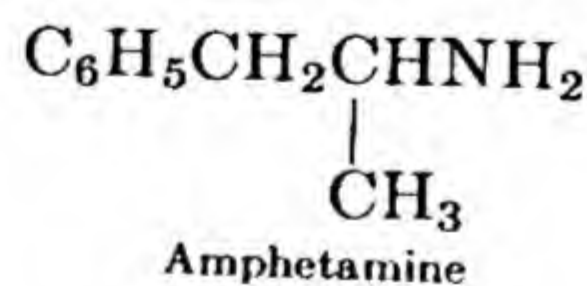
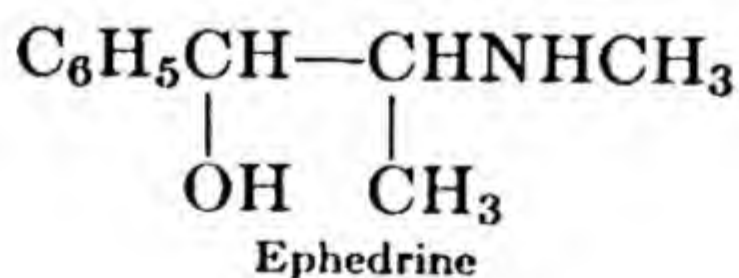
In another method of application the dye is actually manufactured in the fabric. The cloth is soaked in a solution of a phenol in alkali and then in a diazonium solution. Coupling with production of the dye then occurs in the fiber. Such a dye is said to be a developed or ingrain dye. An example is dianisidine blue.



Other types of dyes are discussed in later chapters.

## ► AMINES IN MEDICINE

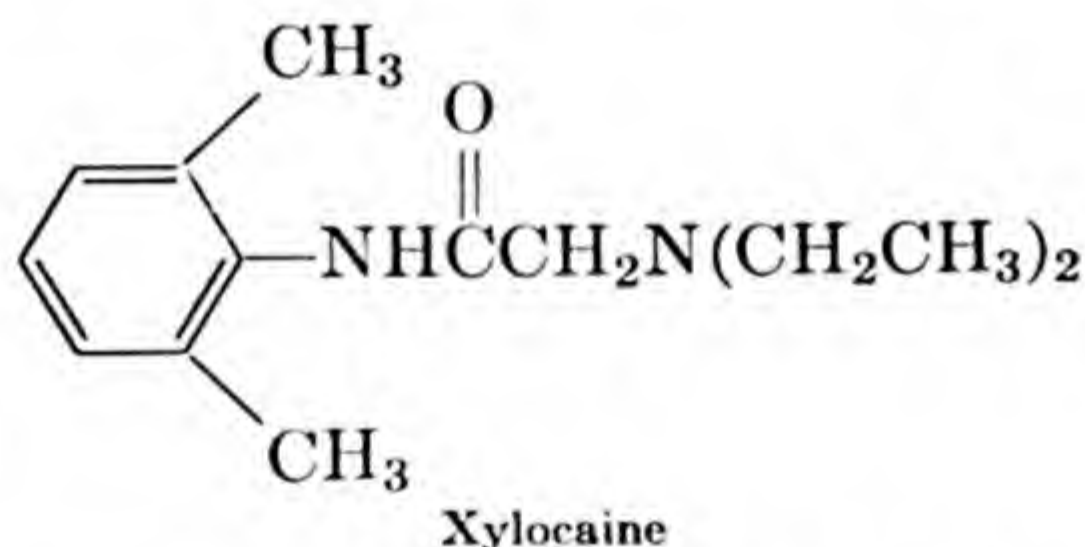
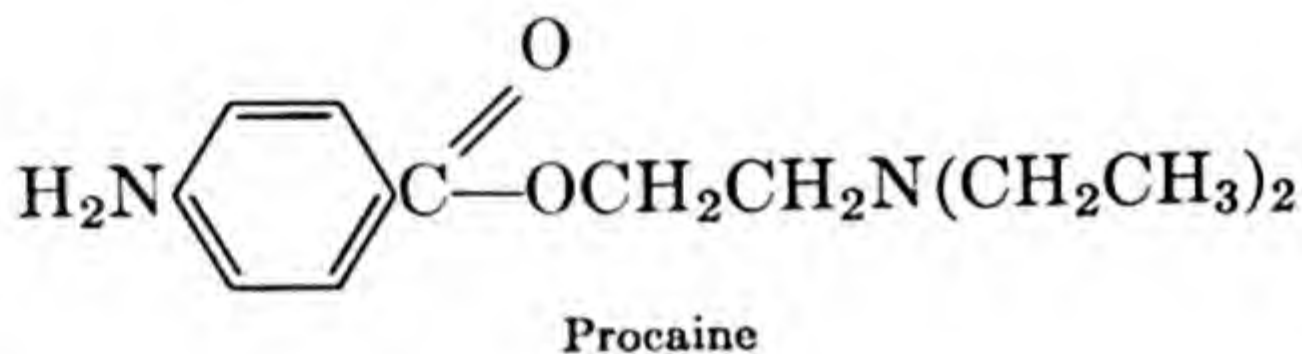
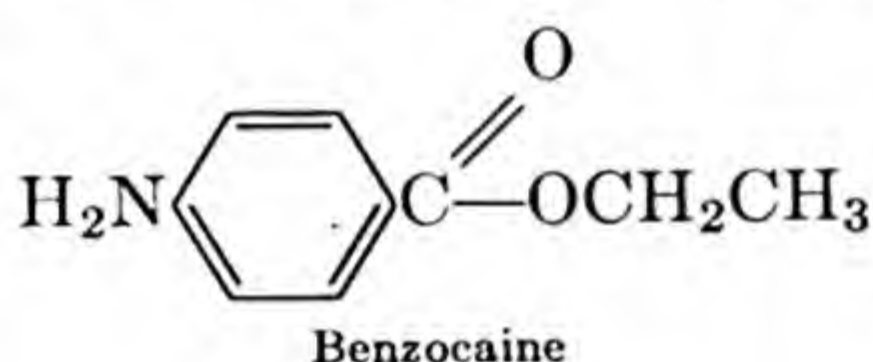
Many organic medicinals contain amino groups. Aside from any physiological effect the amino groups themselves may have, they aid in making the drugs more water-soluble because they can form salts. In fact, drugs are often administered as salts, such as hydrochlorides, malcates, or citrates. Certain types of amines, however, have special physiological effects. It has been found that some derivatives of  $\beta$ -phenylethylamine,  $C_6H_5CH_2CH_2NH_2$ , are useful in combating depressive states. Examples are ephedrine, amphetamine (Benzedrine; Dexedrine), methamphetamine, and mephentermine.



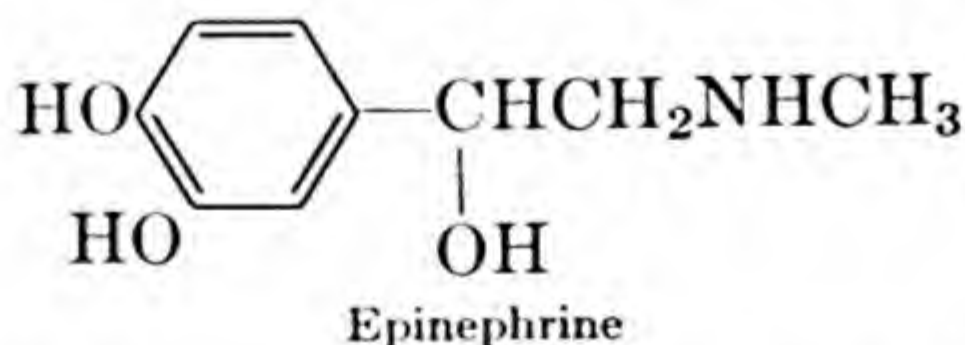


Amines having the physiological properties of these compounds are described as sympathomimetic because they have the effect of stimulating the sympathetic nerves to the organs of the body. They thus cause numerous manifestations, such as increasing the blood pressure, inhibiting intestinal muscular activity, reducing the appetite, increasing alertness, and stimulating the higher sensory centers of the brain. If used excessively, they may produce these effects in the extreme.

The esters of *p*-aminobenzoic acid are widely employed as topical and infiltration anesthetics. Ethyl *p*-aminobenzoate (benzocaine), a component of ointments to relieve itching, and procaine (Novocaine), the well-known dental anesthetic, are examples. Xylocaine, though not a derivative of *p*-aminobenzoic acid, has some similar structural features. Like procaine, it is employed as a dental anesthetic and in minor external surgery.



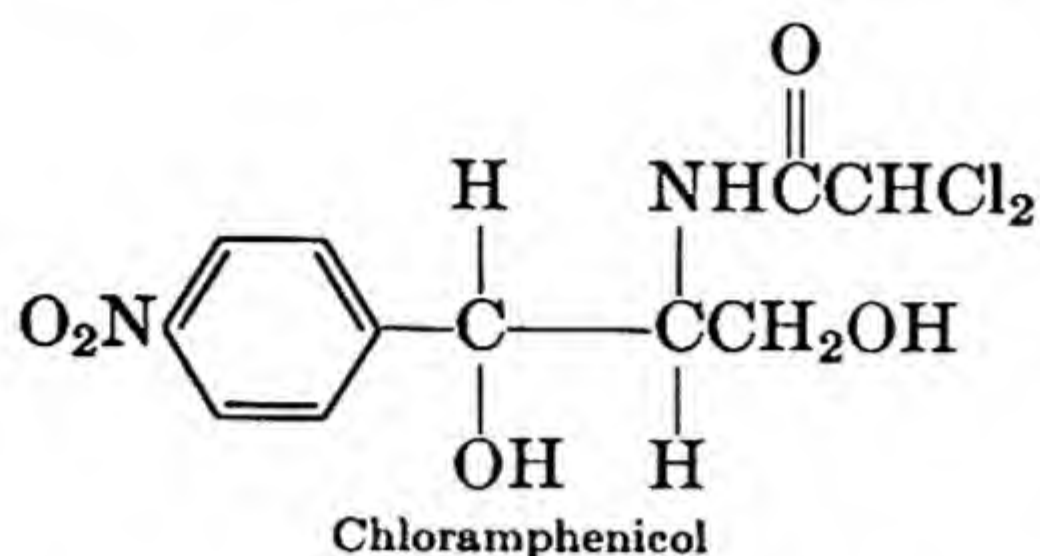
Two other amine derivatives of medical interest are epinephrine and chloroamphenicol. Epinephrine (Adrenalin) is a hormone produced by the adrenal glands. Like the sympathomimetic amines already mentioned, it is a derivative of  $\beta$ -phenylethylamine. Its physiological properties are also similar. It raises the blood pressure and is involved in the conversion of liver glycogen to glucose.



Chloramphenicol (Chloromycetin) was first isolated from a culture of *Streptomyces venezuelae*. It has an especially interesting structure for a natural product in that it possesses a nitro group and a dichloromethyl group, neither of which has previously been encoun-



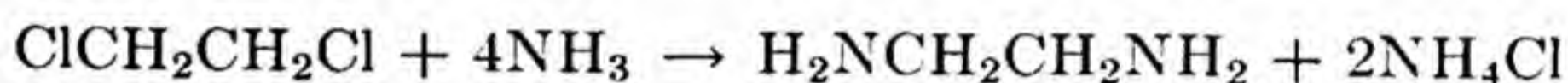
tered in a natural product. Chloramphenicol has been synthesized.



It is a broad-spectrum antibiotic, effective against many bacteria, rickettsiae, and some viruses.

## ► DIAMINES

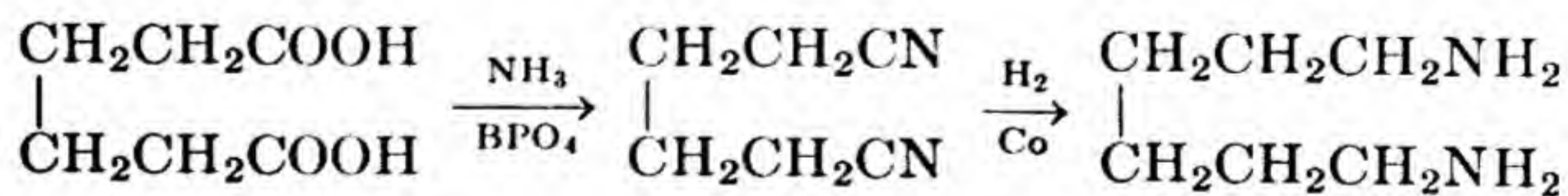
Numerous organic compounds having two amino groups are known; they are called diamines. Ethylenediamine has various applications which depend upon the fact that it is a water-soluble organic base. It is prepared by the reaction of ethylene chloride with ammonia.



The aromatic diamines are valuable as dye intermediates. The *para* compound, *p*-phenylenediamine, is converted by oxidation to a deep brown substance employed as a fur dye.



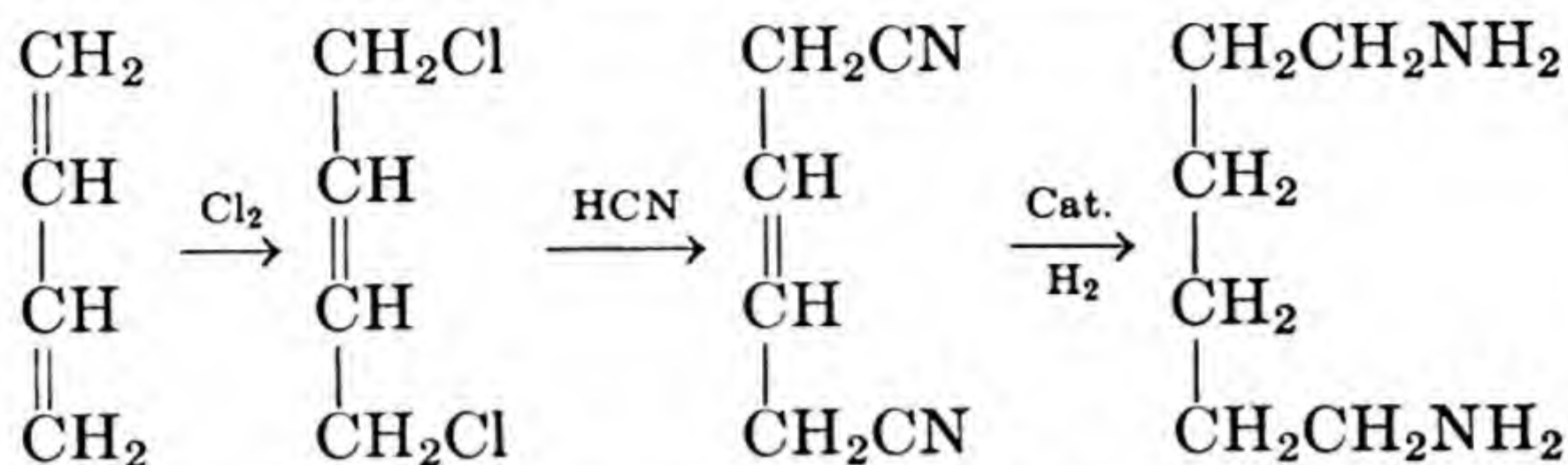
Commercially, the most important diamine is hexamethylenediamine, a nylon intermediate. A number of different nylons are commercial products, but nylon 66 is that manufactured and sold in the largest amount. It is the polyamide from hexamethylenediamine and adipic acid. Several processes have been developed for the preparation of the amine and acid. In the original method both adipic acid (p. 116) and hexamethylenediamine are obtained from phenol. Benzene and cyclohexane can also be used as raw materials. Nickel



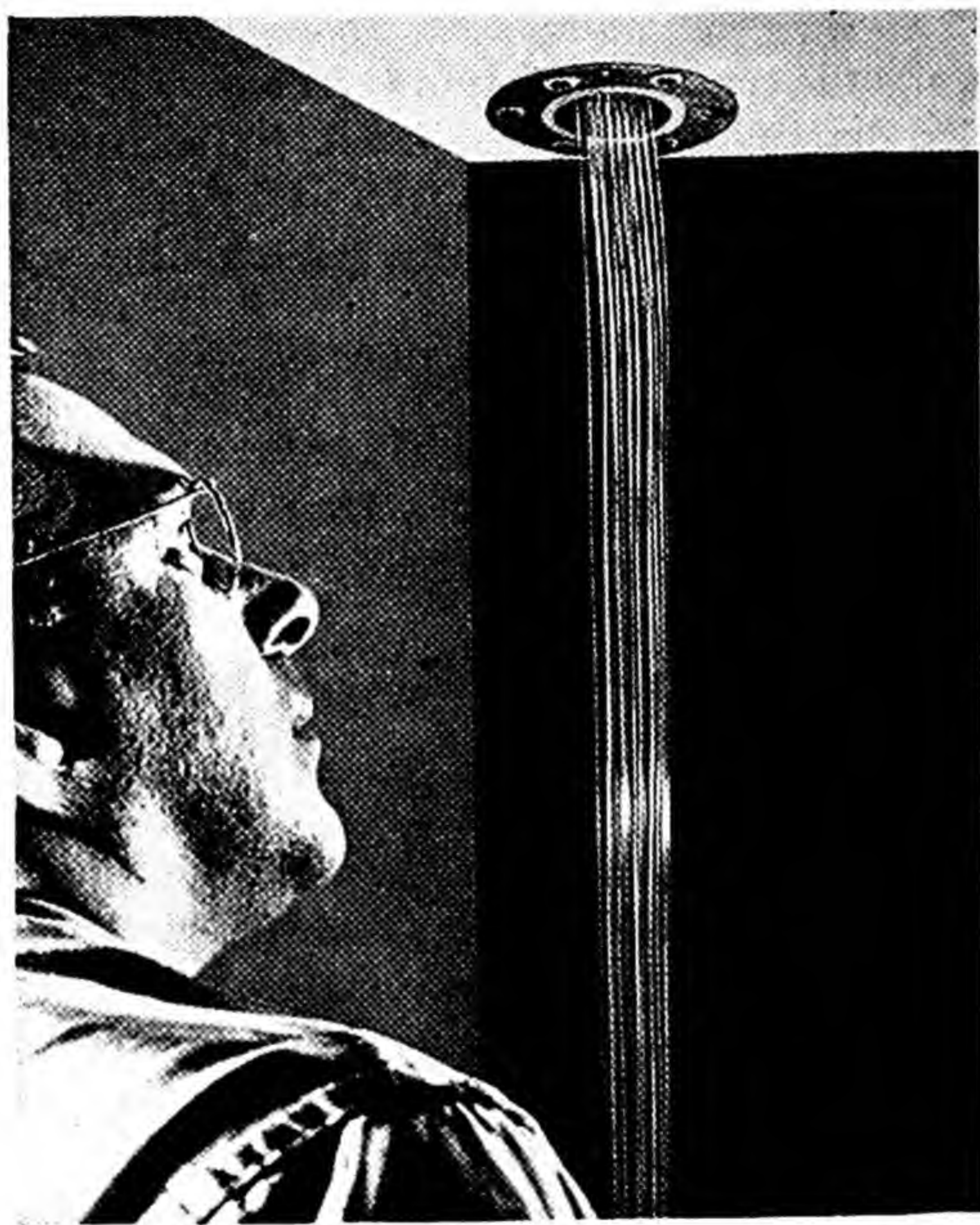
and hydrogen convert benzene to cyclohexane, which is oxidized by



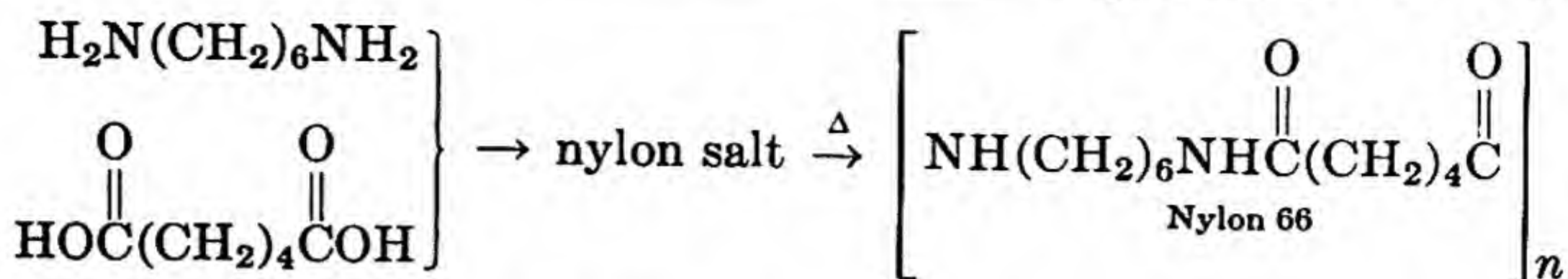
air with a cobalt catalyst to a cyclohexanol-cyclohexanone mixture. Butadiene also provides a source for the diamine.



When the diamine and a dibasic acid (usually adipic acid) are brought together, a salt is formed which contains equimolar amounts of the two components. When the salt is heated, water is evolved, and the polymer, nylon, results.



Spinning nylon filaments. The molten polymer is forced through tiny holes and solidifies as it emerges. All synthetic fibers are formed in essentially this way, though they may be formed from solution rather than from a melt, in which case the filament is formed by rapid evaporation of the solvent. The final product may be monofilament, such as in most ladies' hosiery, tennis racket strings, and toothbrush bristles, or many such filaments may be twisted into a yarn, such as in tire cord. (Photograph furnished by the Du Pont Company.)

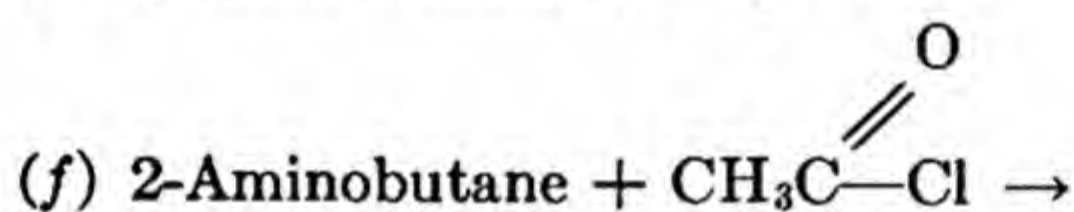
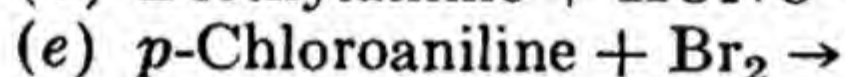
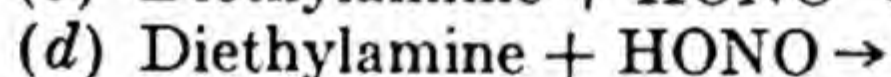
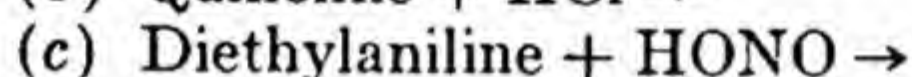
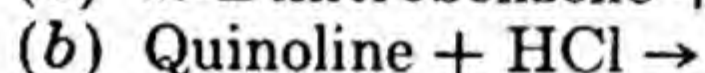
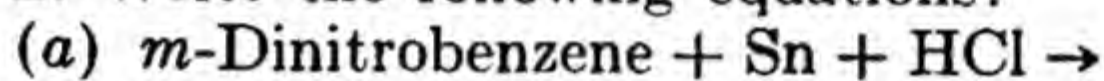


In addition to the familiar applications of nylon as a fiber in clothing, brush bristles, tennis-racket strings, fish lines, and the like, considerable amounts are used in molding compositions for gears, bearings, door closures, and electrical equipment.

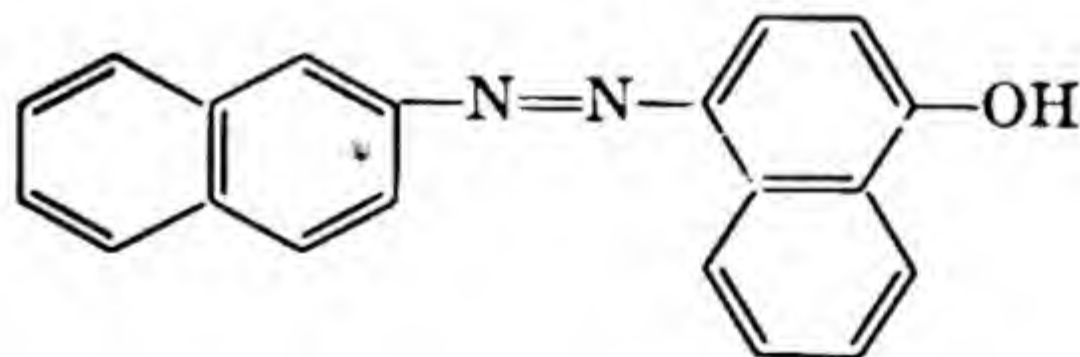
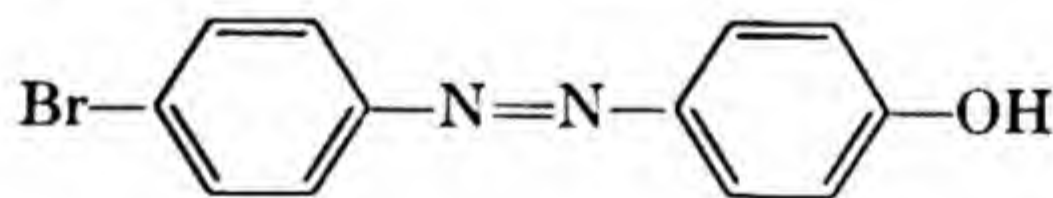
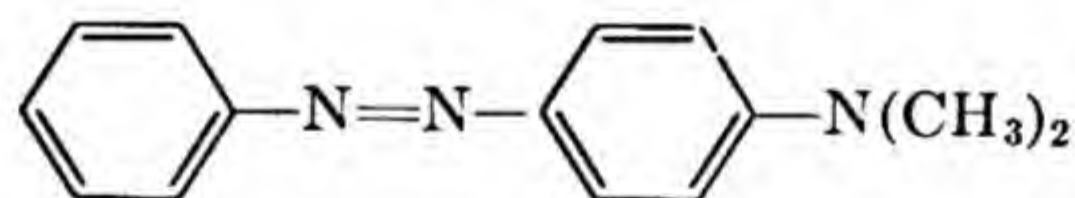
## ► QUESTIONS

1. Why is the differentiation of the three classes of amines by nitrous acid more suitable for aliphatic than aromatic compounds?

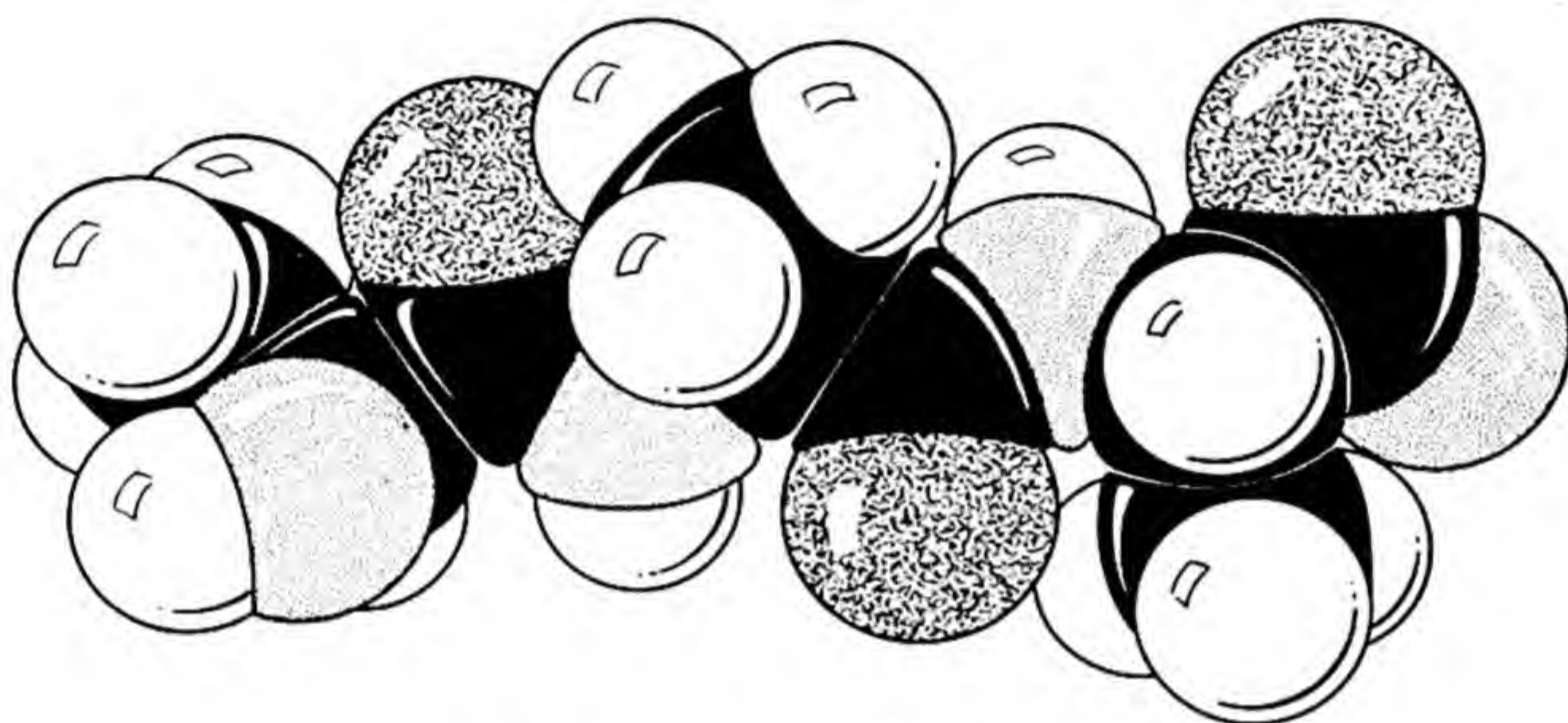
2. Write the following equations:



3. Show how the following compounds could be made.







L-Alanyl Residues in a Peptide Linkage

The model illustrates the peptide linkage ( $\text{—}\overset{\text{O}}{\underset{\text{||}}{\text{C}}}\text{NH—}$ ) by which the amino acid residues in a protein are connected. Three residues from L-alanine and an additional nitrogen atom are shown. The nitrogen atoms at the ends of the chain show where further residues would be attached. Some hydrogen atoms are obscured in the illustration.

Protein materials are found in every part of plants and animal bodies. Skin, hair, nerve tissue, muscles, tendons, nails, horns, hoofs, and feathers are essentially proteins. In plants, however, only the seeds contain appreciable amounts of proteins. Examples of individual proteins are the casein in milk, albumin in eggs, hemoglobin in blood, and gelatin in animal tissues. Our knowledge of the structure of such substances has been gained largely by a study of their hydrolysis products. Proteins have very high molecular weights, and their hydrolysis ultimately produces amino acids. Since they are fundamental to the structure of proteins, a brief consideration of the amino acids is given at this point.



## ► AMINO ACIDS

The amino acids possess at least one amino group and one carboxyl group which make them at once acidic and basic, *i.e.*, amphoteric. The hydrolysis of numerous proteins from widely different sources has revealed that the number of amino acids involved is limited. It will be instructive to examine the structural formulas of those more commonly found. Some, it will be noted, have one amino and one carboxyl group; these, along with cystine which has two of each, are said to be neutral amino acids. Others have two basic groups and one acid group; these are the basic amino acids. A third type has one amino group and two carboxyl groups; these are the acidic amino acids. Two of the amino acids, methionine and cystine, contain sulfur. Some have hydroxyl groups, some have benzene rings, and some, heterocycles. Thus there is considerable variation in type among the amino acids found in nature. More striking, however, are the similarities discernible among these substances. In particular, they are *alpha* amino acids; that is, the amino group and the carboxyl group are held by the same carbon atom. With the exceptions of proline and hydroxypro-

line, all can be represented by 
$$\begin{array}{c} \text{O} \\ \parallel \\ \text{RCHC}-\text{OH} \\ | \\ \text{NH}_2 \end{array}$$
 In all the amino acids

except glycine the *alpha* carbon atom is asymmetric, and optical isomers are therefore possible. Careful hydrolysis of proteins always yields L-amino acids.

The amino acids are white solids, insoluble in most organic solvents. All are soluble in water, although the solubilities of cystine and tyrosine are not high. When heated they gradually undergo browning and decompose without melting. These properties are those of salts, and,

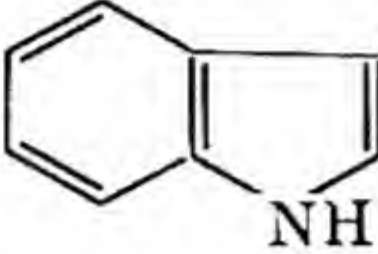
indeed, amino acids are best represented as inner salts 
$$\begin{array}{c} \text{O} \\ \parallel \\ \text{RCHC}-\text{O}^\ominus \\ | \\ \text{NH}_3^\oplus \end{array}$$
 in

which the amino and carboxyl groups have neutralized each other.



## Amino Acids from Protein Hydrolysis

Name	Formula
Glycine	$\begin{array}{c} \text{CH}_2\text{COOH} \\   \\ \text{NH}_2 \end{array}$
Alanine	$\begin{array}{c} \text{CH}_3\text{CHCOOH} \\   \\ \text{NH}_2 \end{array}$
Valine	$\begin{array}{c} (\text{CH}_3)_2\text{CHCHCOOH} \\   \\ \text{NH}_2 \end{array}$
Leucine	$\begin{array}{c} (\text{CH}_3)_2\text{CHCH}_2\text{CHCOOH} \\   \\ \text{NH}_2 \end{array}$
Isoleucine	$\begin{array}{c} \text{CH}_3\text{CH}_2\text{CH}-\text{CHCOOH} \\   \quad   \\ \text{CH}_3 \quad \text{NH}_2 \end{array}$
Phenylalanine	$\begin{array}{c} \text{C}_6\text{H}_5-\text{CH}_2\text{CHCOOH} \\   \\ \text{NH}_2 \end{array}$
Tyrosine	$\begin{array}{c} \text{HO}-\text{C}_6\text{H}_4-\text{CH}_2\text{CHCOOH} \\   \\ \text{NH}_2 \end{array}$
Serine	$\begin{array}{c} \text{HOCH}_2\text{CHCOOH} \\   \\ \text{NH}_2 \end{array}$
Threonine	$\begin{array}{c} \text{CH}_3\text{CH}-\text{CHCOOH} \\   \quad   \\ \text{OH} \quad \text{NH}_2 \end{array}$
Methionine	$\begin{array}{c} \text{CH}_3\text{SCH}_2\text{CH}_2\text{CHCOOH} \\   \\ \text{NH}_2 \end{array}$
Cystine	$\begin{array}{c} \text{SCH}_2\text{CHCOOH} \\   \quad   \\ \text{NH}_2 \quad \text{NH}_2 \\   \quad   \\ \text{SCH}_2\text{CHCOOH} \\   \\ \text{NH}_2 \end{array}$
Proline	$\begin{array}{c} \text{CH}_2-\text{CH}_2 \\   \quad   \\ \text{CH}_2 \quad \text{CHCOOH} \\ \diagdown \quad \diagup \\ \text{NH} \end{array}$

Name	Formula
Hydroxyproline	$  \begin{array}{c}  \text{HOCH} - \text{CH}_2 \\    \quad \quad   \\  \text{CH}_2 \quad \text{CHCOOH} \\  \diagdown \quad \diagup \\  \text{NH}  \end{array}  $
Tryptophan	$  \begin{array}{c}  \text{CH}_2\text{CHCOOH} \\    \\  \text{NH}_2  \end{array}  $ 
Lysine	$  \begin{array}{c}  \text{H}_2\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CHCOOH} \\    \\  \text{NH}_2  \end{array}  $
Arginine	$  \begin{array}{c}  \text{H}_2\text{NC}(\text{NH})\text{CH}_2\text{CH}_2\text{CH}_2\text{CHCOOH} \\     \quad \quad   \\  \text{NH} \quad \quad \text{NH}_2  \end{array}  $
Histidine	$  \begin{array}{c}  \text{N} - \text{C} - \text{CH}_2\text{CHCOOH} \\     \quad    \quad   \\  \text{HC} \quad \text{CH} \quad \text{NH}_2 \\  \diagdown \quad \diagup \\  \text{NH}  \end{array}  $
Aspartic acid	$  \begin{array}{c}  \text{CH}_2 - \text{CHCOOH} \\    \quad   \\  \text{COOH} \quad \text{NH}_2  \end{array}  $
Glutamic acid	$  \begin{array}{c}  \text{CH}_2\text{CH}_2\text{CHCOOH} \\    \quad   \\  \text{COOH} \quad \text{NH}_2  \end{array}  $

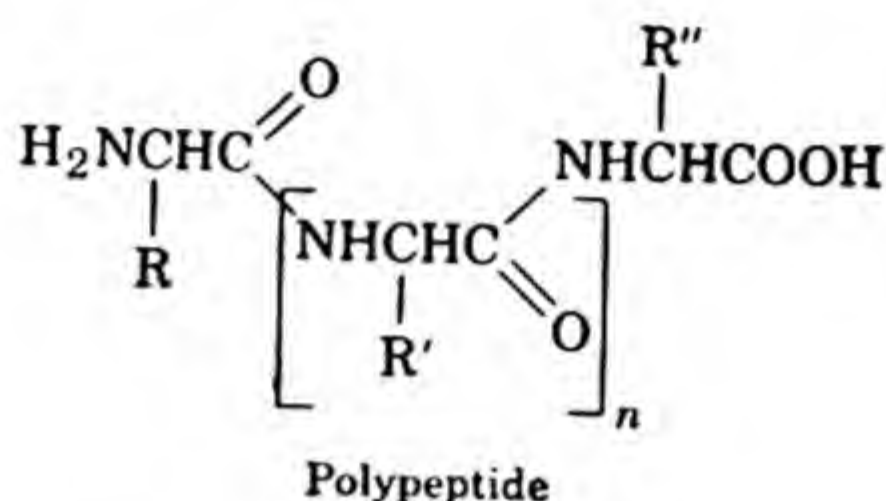
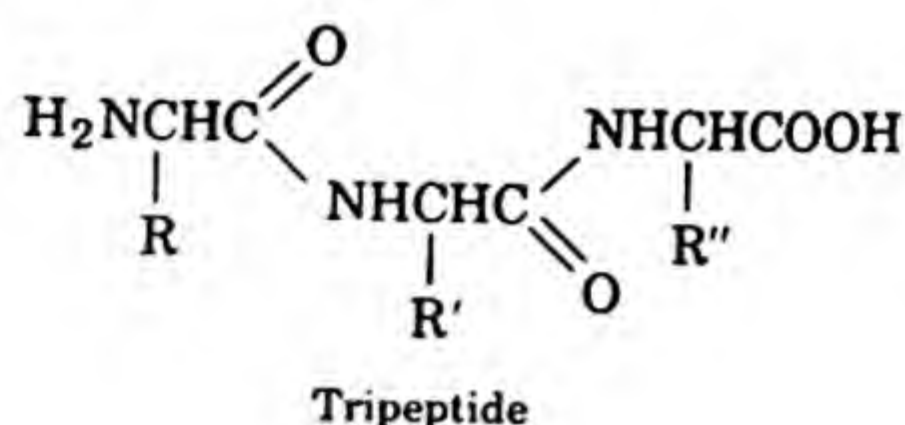
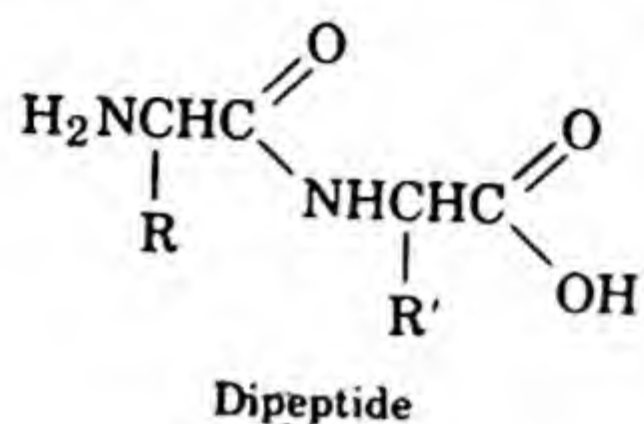
## ► PROTEINS

**The Structure of Proteins.** Analyses show that there is considerable variation in the number and amount of amino acids produced in protein hydrolysis. Some proteins, such as casein and serum albumin, yield nearly all of the amino acids. Others, such as salmin, produce only six or so different kinds. Some proteins are the source of especially large amounts of a particular amino acid. Silk fibroin, for example, yields over 40% glycine. In spite of these variations, nitrogen analyses of numerous proteins show that nearly all of them contain 15 to 18% of that element. This characteristic is found to be useful in the analyses of feeds for animals. The percentage of nitrogen obtained by analysis is multiplied by the factor 6.25, and the product is presumed to be the percentage of protein in the sample.

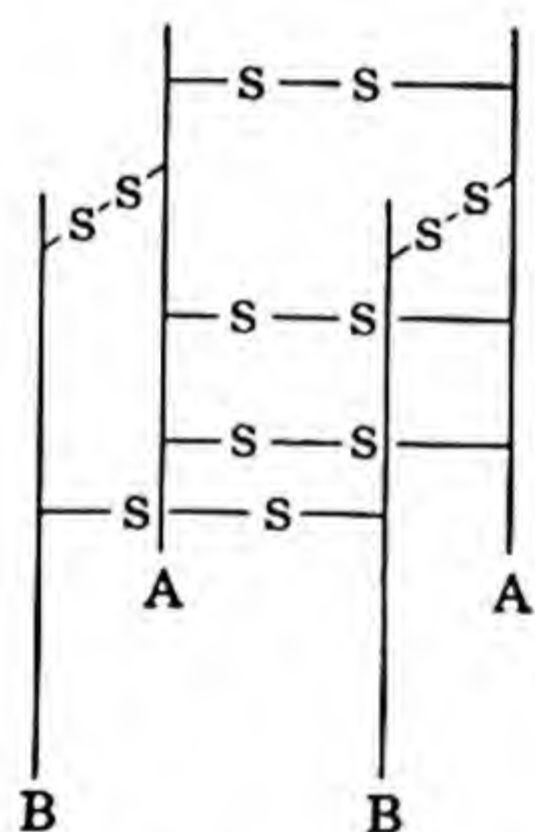
Because of their mode of production from proteins it is logical to assume that the amino acids are joined together by amide linkages.



Though no protein has been synthesized, low-molecular-weight compounds of similar structure have been. They are said to be dipeptides if they have two amino acid residues, tripeptides if they have three, polypeptides if they have many.



It is easy to see how the amino acids can be formed in the hydrolysis of proteins by the cleavage of the amide (peptide) linkages and addition of the elements of water. The synthesis of higher peptides is difficult; they cannot be made directly from the amino acids. The largest synthetic peptide so far reported contains nineteen amino acid residues.



The insulin molecule contains four polypeptide chains which are joined by the disulfide linkages of cystine. There are two types of chains (labeled A and B) in the molecule. The A chains have 21 amino acid residues and the B chains, 30.

**Schematic Representation of the Insulin Molecule**

It is possible to picture a protein as a long series of amino acid residues in a straight chain, but most proteins appear to be more complex. For example, since cystine has two carboxyl and two amino groups, it can participate in two such chains, thus linking them together.





as the *xanthoproteic test*. The yellow color which appears when concentrated nitric acid comes in contact with the skin is an example of this test. The biuret test, previously mentioned, is positive for many proteins, but some other substances also give the test. The ninhydrin reagent gives colors with proteins and their hydrolysis products, including the amino acids.

**Coagulation and Precipitation of Proteins.** An important property of water-soluble proteins is their tendency to form precipitates, known as *coagulated proteins*, under the influence of heat, ultraviolet radiation, alcohol, or supersonic vibrations. The hardening of egg albumin is a phenomenon familiar to everyone. The mild action of acids or bases on proteins brings about a less profound change. The products are said to be *denatured proteins*; they do not dissolve in neutral solutions but are soluble in aqueous acids or bases. Many of the salts of heavy metals convert proteins into insoluble substances. The poisonous nature of the salts of mercury, lead, and silver has been attributed to their reaction with the proteins of the body. On the other hand, and for the same reason, egg white is a recommended antidote for heavy metal poisoning. A number of other substances, such as phosphomolybdic acid, picric acid, and tannic acid, also produce precipitates with soluble proteins. In the preparation of leather chromium salts and tannic acid are employed to change the protein of the skin into less soluble materials.

**Classification of Proteins.** Proteins that give only  $\alpha$ -amino acids on hydrolysis are called *simple proteins*. Their hydrolysis proceeds through several indistinct phases. The higher molecular weight materials are called, in order, proteoses, peptones, and polypeptides. These together with other substances obtainable from proteins (such as coagulated and denatured proteins) are said to be *derived proteins*.

The simple proteins are classified largely upon their solubility behavior. For example, albumins are soluble in water. Globulins, though insoluble in water, are soluble in half-saturated ammonium sulfate solutions. Most proteins which are insoluble in water are soluble in dilute acids or alkalies, but some are soluble only in alkali or only in acid.

Some proteins found in nature are combined with nonprotein materials. Such substances are said to be *conjugated proteins*, and they are classified in accordance with the nature of the nonprotein portion of the molecule. Some types are glycoproteins, such as mucin in the saliva, which give a sugar on hydrolysis, chromoproteins, such as hemoglobin, which yield a colored substance, and nucleoproteins, which are found in all cell nuclei and produce upon hydrolysis a



nucleic acid, an exceptionally complex type of substance in its own right.

**Digestion and Metabolism of Proteins.** The digestion of proteins begins in the stomach under the influence of two enzymes of the gastric juice. One of these, *rennin*, converts casein from ingested milk into a soluble and an insoluble portion. The other, *pepsin*, is secreted in an inactive form, *pepsinogen*, which is converted to the active form by the hydrochloric acid of the stomach. Pepsin catalyzes the hydrolysis of proteins to proteoses and peptones. The hydrolysis of proteins is completed in the small intestine, and the products are amino acids. Two of the enzymes responsible are produced by the pancreas, but in the inactive form. These are *trypsinogen* and *chymotrypsinogen*; the former is converted into the active enzyme *trypsin* by *enterokinase*, an enzyme present in the intestinal juice. Trypsin in turn catalyzes the conversion of chymotrypsinogen into *chymotrypsin*. The two active enzymes convert proteins into lower-molecular-weight peptides. Complete hydrolysis to  $\alpha$ -amino acids is accomplished by *carboxypolypeptidase*, produced by the pancreas, and by *aminopolypeptidase* and *dipeptidase* from the intestinal mucosa.

The intestinal wall is permeable to amino acids, but not to peptides. Indeed, if proteins, peptones, or proteoses are absorbed by the blood stream, severe shock may result. Sensitivities of some individuals toward protein foods, such as eggs, are due to conditions in which some of the products of incomplete hydrolysis are absorbed.

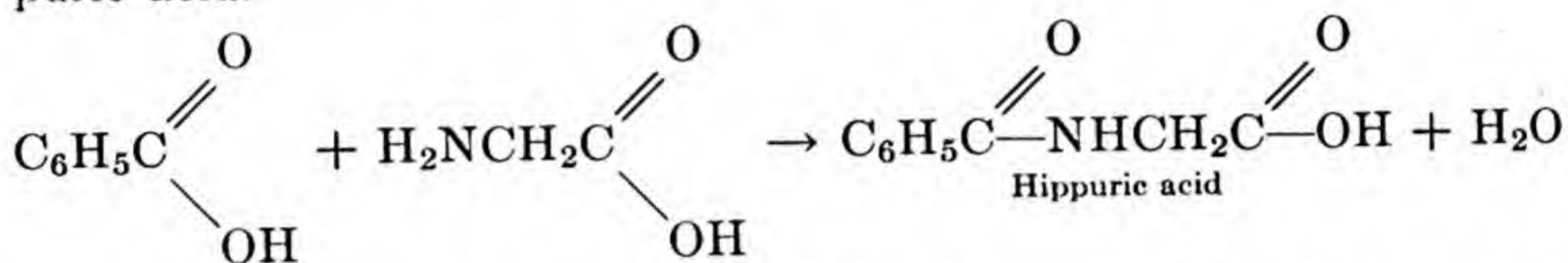
The amino acids absorbed by the blood are removed very rapidly by the tissues. Their ultimate fate may be any of the following: (1) conversion into body protein, (2) oxidation to provide energy, as with carbohydrates and fats, and (3) transformation into carbohydrates, fats, hormones, enzymes, or other vital products.

The mechanism of the conversion of the amino acids into proteins is unknown, but it undoubtedly occurs at the site at which the protein is to be used. It may be that the same enzymes responsible for the hydrolysis of proteins are instrumental in their synthesis. A remarkable point is that there are some eight or nine amino acids which the body cannot synthesize from other amino acids or from nonprotein material. These are valine, leucine, isoleucine, phenylalanine, methionine, threonine, lysine, tryptophan, and possibly arginine. These are said to be "essential amino acids" and must be eaten, normally in the form of protein. Because certain of these amino acids are absent in some proteins it becomes apparent that some proteins are better foods than others.



Amino acids above the amount necessary for the synthetic requirements of the body can be oxidized to provide energy. In addition to water and carbon dioxide, urea and ammonia are products of this oxidation. Certain amino acids are convertible to fats and others to carbohydrates and may be stored for later energy demands in these forms.

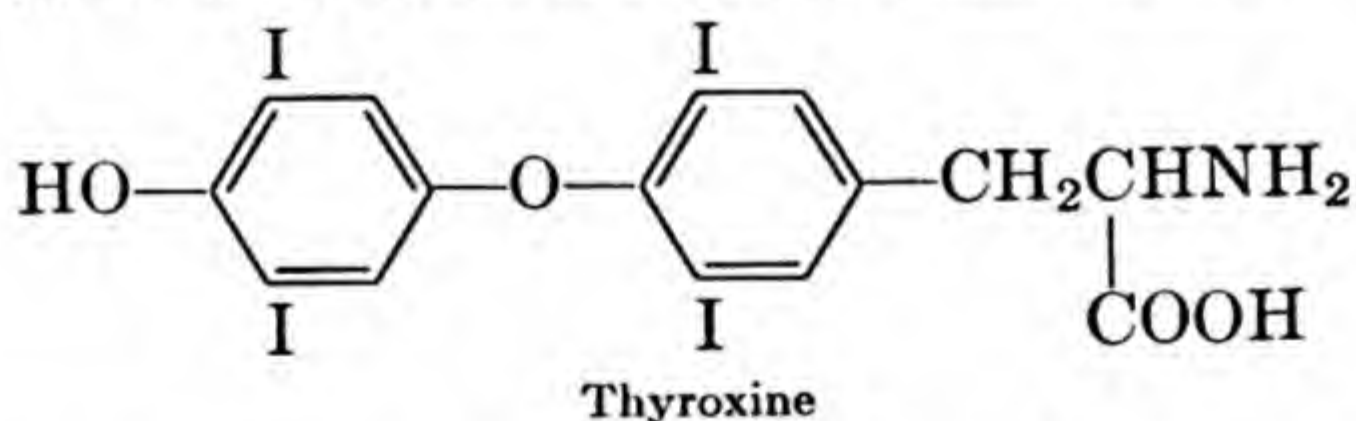
Certain amino acids have special functions in the body. For example, cystine and particularly glycine function as detoxifiers. Benzoic acid, which occurs in many foods, is thus converted into hippuric acid.



Arginine has a special function in that it is involved in the conversion of ammonia and carbon dioxide into urea.

## ► PROTEINLIKE NATURAL PRODUCTS

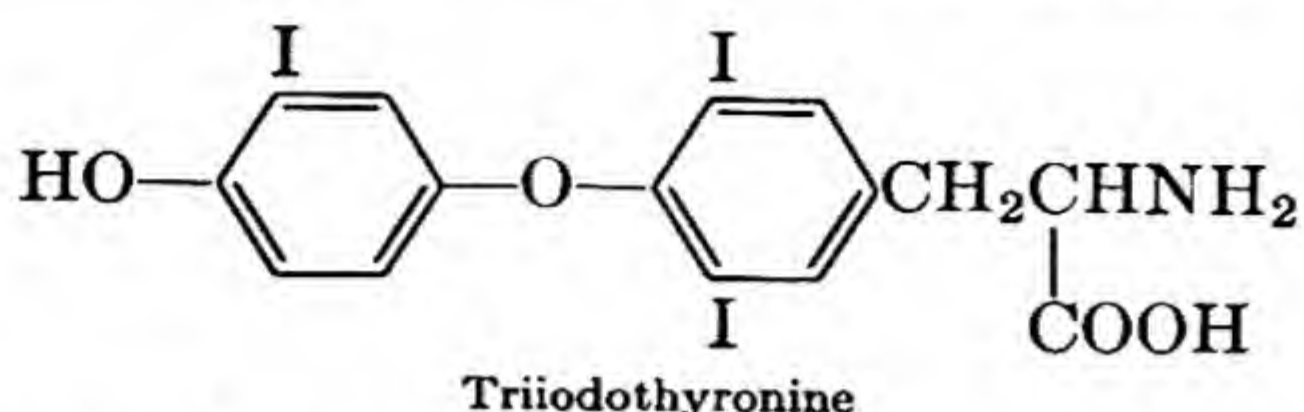
**Hormones.** Hormones are involved in the control of various functions of the body. They are secreted by the ductless glands and are transported by the blood. All of them are organic substances and some of them are proteins or proteinlike. *Thyroglobulin*, produced in the thyroid gland, is involved in the general metabolic control of the body. It is a high-molecular-weight protein which upon hydrolysis yields thyroxine as well as the usual amino acids. The body can



synthesize thyroxine from phenylalanine or tyrosine, but iodides are also necessary. In regions in which there is a deficiency of iodides in the diet insufficient thyroxine is produced. This may lead to various disorders, of which endemic goiter is best known. Individuals suffering from a deficiency of thyroglobulin can be treated with extracts prepared from the thyroid glands of cattle or with synthetic thyroxine.

Evidence has accumulated that the true hormone of the thyroid gland is the amino acid *triiodothyronine*. Tests show its activity to be several times that of thyroxine.





The hormones produced by the pituitary gland are proteins. Some of them exert control over other ductless glands. The adrenocorticotrophic hormone (ACTH), for example, controls adrenal cortex secretions. It has been used in the treatment of arthritis. The posterior portion of the pituitary produces two hormones which are cyclic nonapeptides. One of them, *pitressin*, has control over water retention by the body, and the other, *pitocin*, is concerned with labor during parturition. The parathyroids, of which there are usually four, produce a hormone which is a proteinlike substance. It is concerned with the retention of calcium and phosphate by the body and therefore is associated with bone formation.

A special tissue of the pancreas, the isles of Langerhans, produces the hormone insulin, which is a protein containing zinc. Its structure is known with a high degree of certainty. In humans with insufficient insulin the result is diabetes, the commonest of all hormone deficiency diseases. The symptoms are a loss in weight, increase in the glucose content of the blood, excretion of glucose in the urine, and the appearance of acetone and related compounds in the blood and urine. The patient also ingests large amounts of water because of a burning thirst and thus excretes more than the usual amount of urine. Both carbohydrate and fat metabolism are impaired. Diabetes is not always a result of a defect of the pancreas but may be due to overactivity of the enzyme insulinase. The symptoms of diabetes can be controlled by injection of insulin, obtained from the pancreas of cattle. Insulin itself, however, can result in the decrease of the blood-sugar level to such an extent that convulsions may result. Certain complexes of proteins with insulin are used to minimize this effect by allowing the insulin to be set free only slowly.

Insulin controls the conversion of glucose into glycogen and fat. Glucagon, a polypeptide hormone, is concerned with the mobilization of liver glycogen.

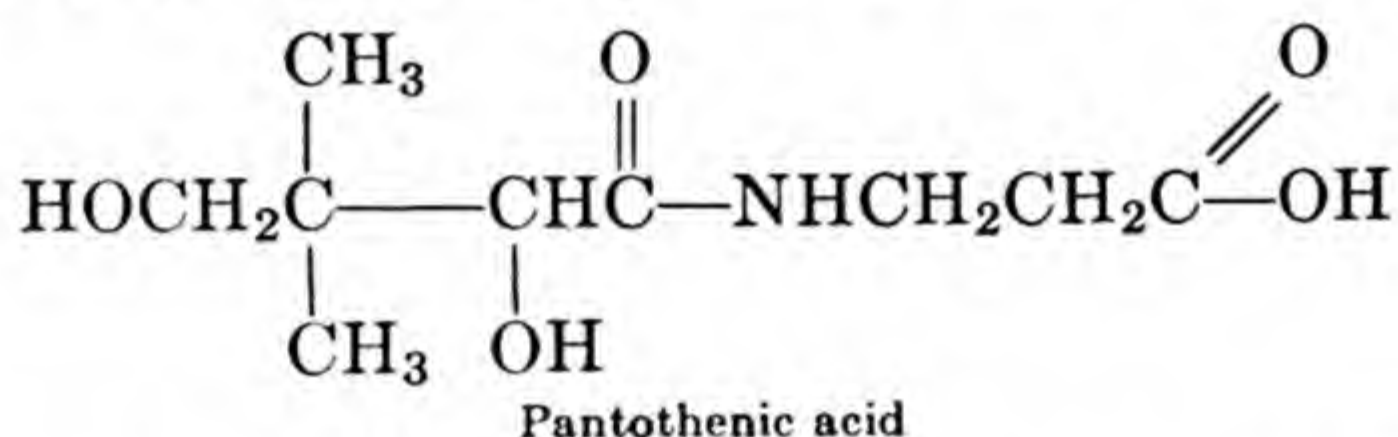
**Enzymes.** Enzymes are the catalysts in living matter and are involved in nearly all biochemical processes. They are remarkable in their specificity, efficiency, and sensitivity toward changes in acidity and temperature. Little is known about the mechanisms by which the enzymes accomplish changes. Most of them are involved in hydrolytic reactions or in oxidation-reduction processes. The hy-



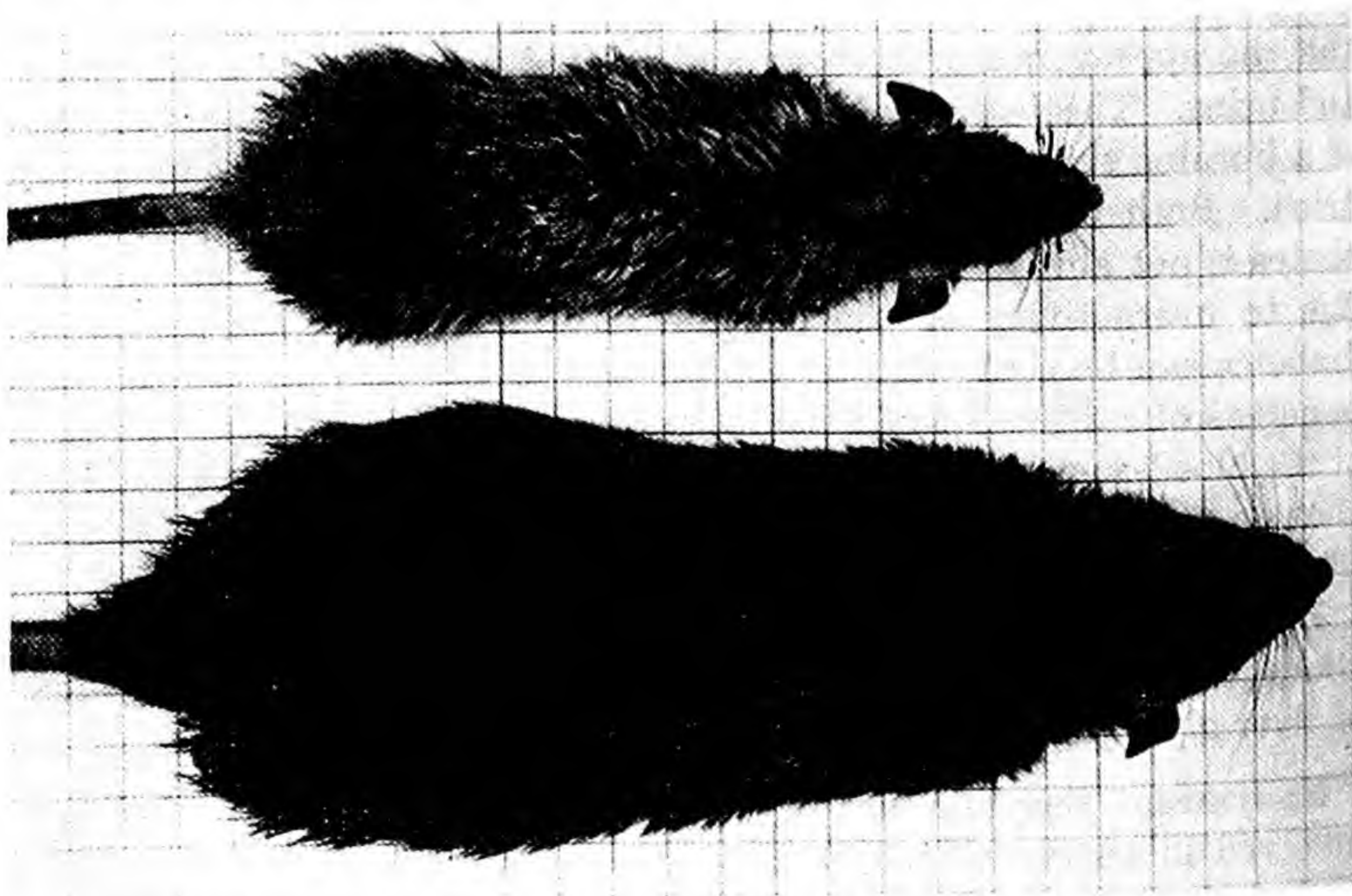
drolytic enzymes appear to be simple proteins, but those which catalyze oxidation-reduction reactions are conjugated proteins. The non-protein part of such an enzyme is called a "coenzyme." The structures of some are known, and it may be that each of the B-vitamins forms part of the structure of a coenzyme.

Pantothenic acid, one of the B-vitamins, is in itself a derivative of the amino acid  $\beta$ -alanine,  $\text{H}_2\text{NCH}_2\text{CH}_2\text{C}$   $\begin{array}{c} \text{O} \\ \parallel \\ \text{OH} \end{array}$ , which does not occur

as a hydrolysis product of proteins. Little is known of the requirements of man for pantothenic acid in the diet. No specific deficiency



disease associated with pantothenic acid is known, but it is likely that multiple deficiencies involving it occur.



Normal and pantothenic acid-deficient rats. The small size, graying of hair, and deposition on the whiskers are typical of pantothenic acid deficiencies in rats. Such animals are almost always shorter-lived. (Photograph courtesy of Merck and Company.)



**Viruses.** Many diseases are transmitted by viruses which can pass through filters so fine that the most minute bacteria are removed. Some of these filterable viruses have been isolated in crystalline form. Investigation has shown that these crystalline viruses are nucleoproteins of very high molecular weight. For example, the virus responsible for the mosaic disease of tobacco has a molecular weight of about 60,000,000. Such virus proteins are unable to reproduce when separated from living matter of the host.

**Polypeptide Antibiotics.** Certain species of bacteria produce the polypeptide antibiotics. The five polymyxins, obtained from *Bacillus polymyxa* and *Bacillus aerosporus*, are polypeptides of molecular weight 1000 to 1300. Upon hydrolysis they yield amino acids and

the branched-chain acid  $\text{CH}_3\text{CH}_2\underset{\text{CH}_3}{\text{CH}}\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\overset{\text{O}}{\underset{\parallel}{\text{C}}}-\text{OH}$ . Poly-

myxin B appears to be the most effective. It has been used in the treatment of whooping cough, intestinal disturbances in children, typhoid fever, and infections caused by *Bacillus pyocyaneus*.

Bacitracin is produced by *Bacillus subtilis*. It is a polypeptide of molecular weight of about 7000. It is especially effective against Gram-positive bacteria, but because of its chemical nature bacitracin is used primarily in external infections, such as skin, eye, nose, and throat infections, especially those caused by streptococcus or staphylococcus organisms.

Tyrothricin is produced by the soil organism *Bacillus brevis*. It is a mixture of two polypeptides, gramicidin and tyrocidin, the first of which is the more effective. It is employed topically, chiefly for skin infections such as impetigo.

It is interesting that the polypeptide antibiotics yield some D-amino acids on hydrolysis, whereas those produced in the hydrolysis of proteins belong to the L-series.



▶ **QUESTIONS** 

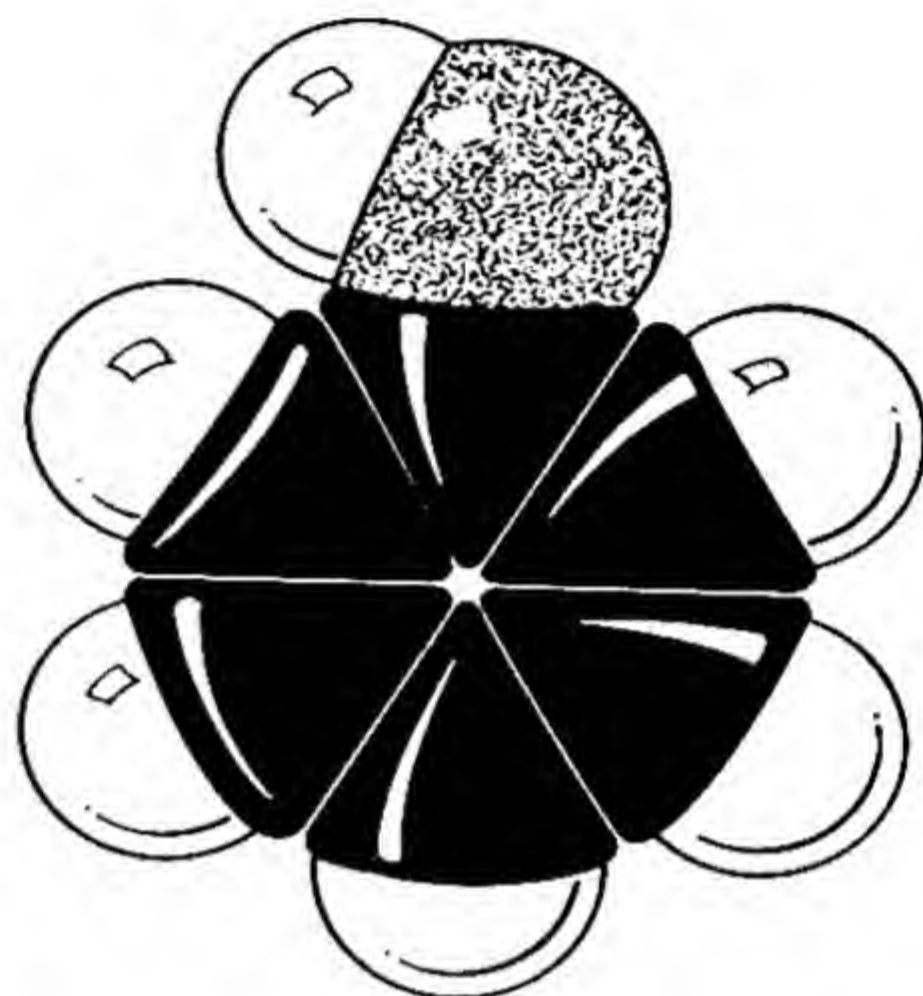
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1. Suppose that a dipeptide yields alanine and valine upon hydrolysis. Write the two possible structural formulas.

2. It is believed that many of the symptoms of allergy are caused by histamine, which can be produced by the loss of carbon dioxide from histidine. Write an equation for the reaction.

3. If rats are fed no protein, but a mixture of amino acids instead, they remain healthy and grow well. If methionine is omitted from the amino acid diet, they do not grow at the usual rate and develop various symptoms of illness. If only cystine is omitted, the rats prosper well. What conclusions can be drawn from these experiments?

4. Suppose the conditions are similar to those in Question 3. The rats are now fed all the amino acids, but the methionine contains radioactive sulfur. The protein of rats fed on this diet is found to contain cystine in which the sulfur is radioactive. What additional conclusion can be drawn?



The hydroxyl group attached to the aromatic ring has properties different from the group attached to an aliphatic chain. The model shows phenol, the simplest aromatic hydroxy compound.

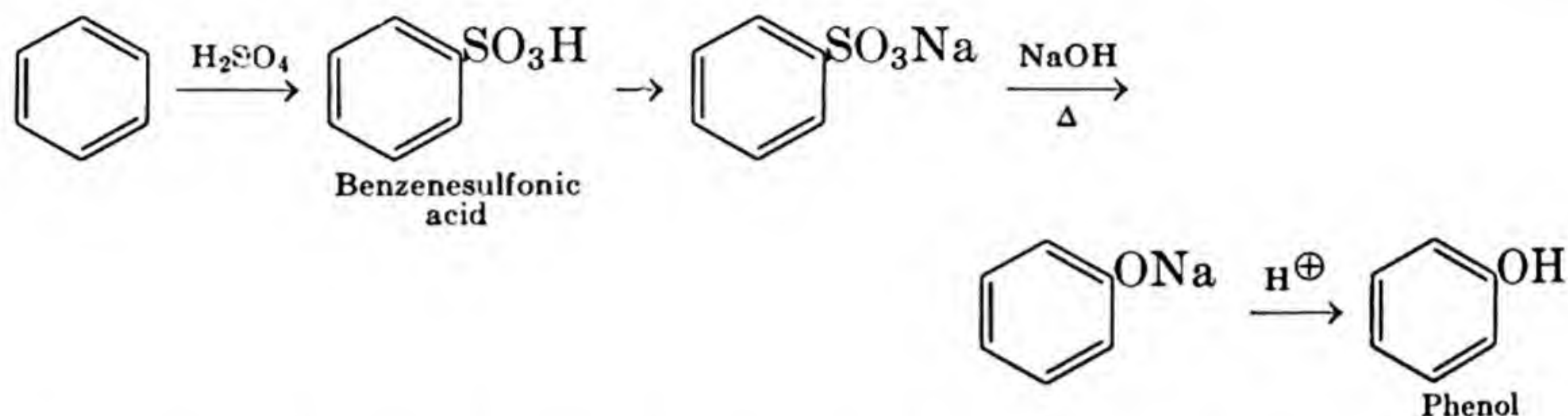
A phenol is a compound that has a hydroxyl group attached to an aromatic ring. The properties of the phenols are considerably different from those of the alcohols. For instance, the phenols are acidic and dissolve readily in aqueous sodium hydroxide, though not usually in aqueous sodium bicarbonate.

### ► PHENOL

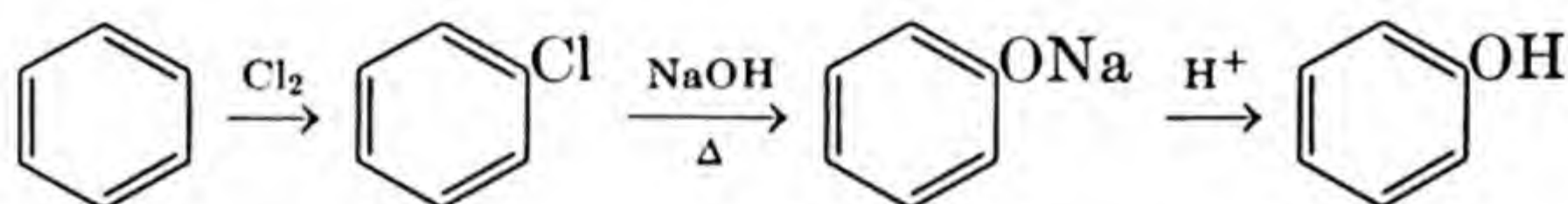
As we have seen, phenols are formed when diazonium salts decompose in the presence of water (Chapter 14). This process is sometimes used in the laboratory for preparing certain members of the series, but never commercially. Though phenol itself is obtained in



small amounts in coal-tar distillation, most of it is made by processes which use benzene as the starting material. In one of these benzene is first sulfonated to give benzenesulfonic acid, a salt of which is fused with alkali to yield sodium phenoxide; upon treatment with acid the phenoxide is converted into phenol.

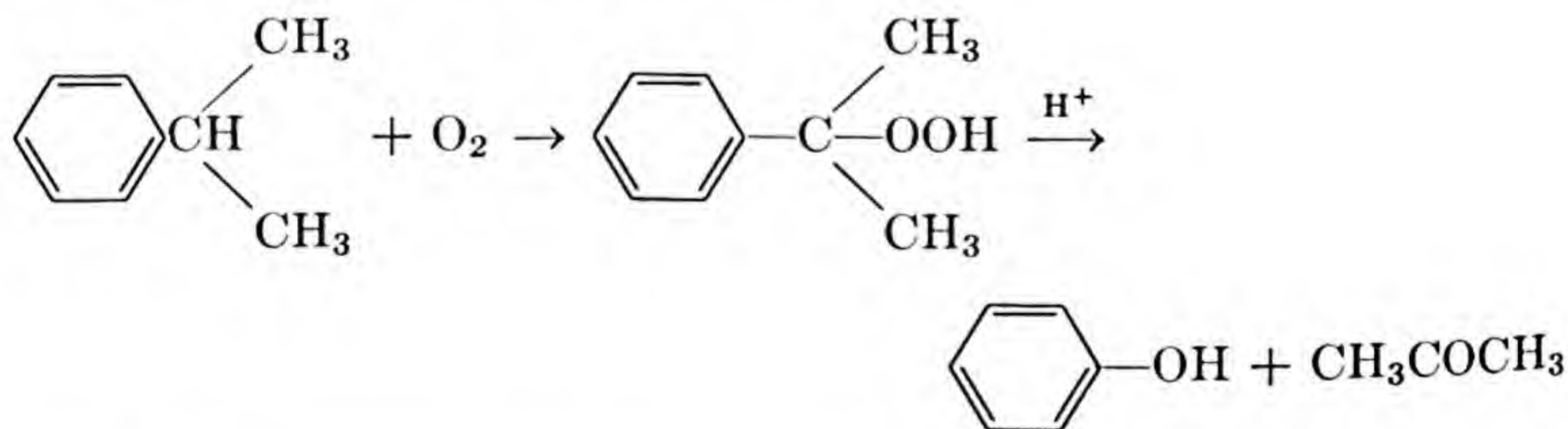


This general process is used for making other phenols as well. In another commercial process chlorobenzene is heated with aqueous alkali under high temperature and pressure.



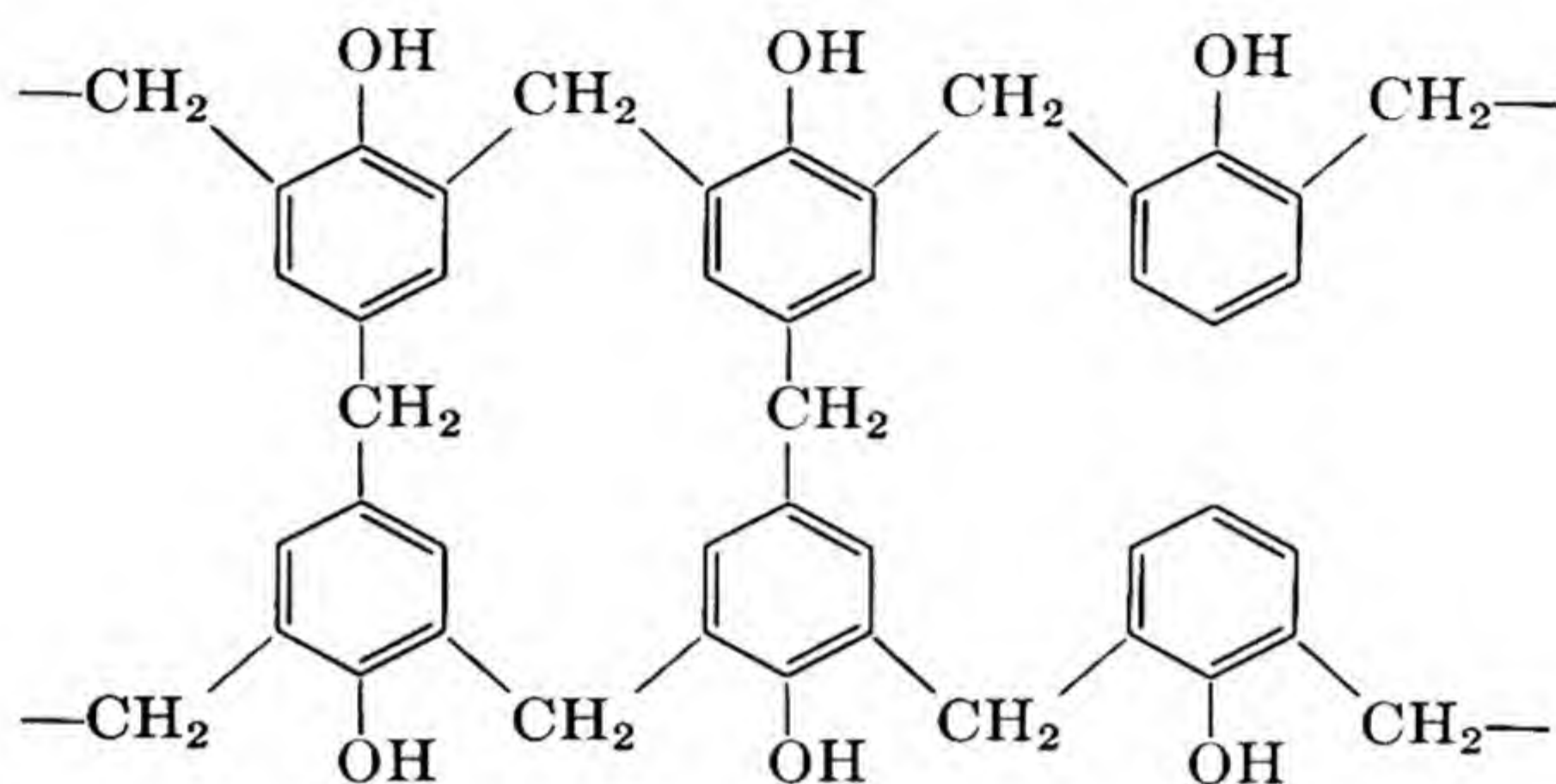
A third process, apparently similar to the second, uses benzene, hydrogen chloride, oxygen (of the air), and water as raw materials. It is likely that chlorine, produced by reaction of hydrogen chloride with oxygen, reacts with the benzene to produce chlorobenzene, which is then hydrolyzed by the water. A high temperature and a catalyst are necessary for this purpose.

In the newest process cumene (isopropylbenzene, made from benzene and propylene by the Friedel-Crafts reaction, p. 46) is oxidized with air to yield a hydroperoxide which is converted to phenol and acetone by mild acid treatment.



Phenol, frequently known as carboic acid, crystallizes in long white needles which melt at  $41^\circ$ . Small amounts of water lower its

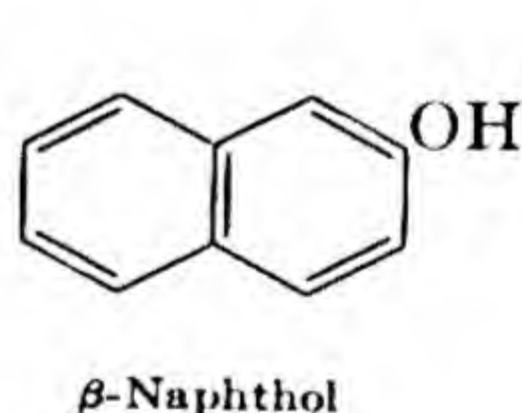
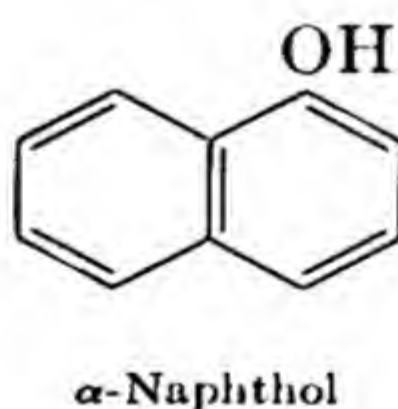
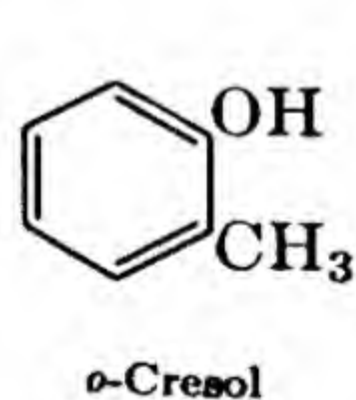
melting point to a value below room temperature, and phenol can be bought in this condition as a liquid. Phenol is corrosive to the skin but has strong antiseptic powers; in fact, other antiseptics are often rated by comparison with it. The *phenol coefficient* represents the efficiency of the antiseptic under consideration versus phenol. Though considerable quantities of phenol are used in the synthesis of medicinal, dyes, and other products, its largest single use is in the manufacture of resins of the Bakelite type. These are produced by the condensation of phenol with formaldehyde. Their essential structure may be represented as follows:



Bakelite is thus a cross-linked polymer and in this respect resembles the urea-formaldehyde polymers.

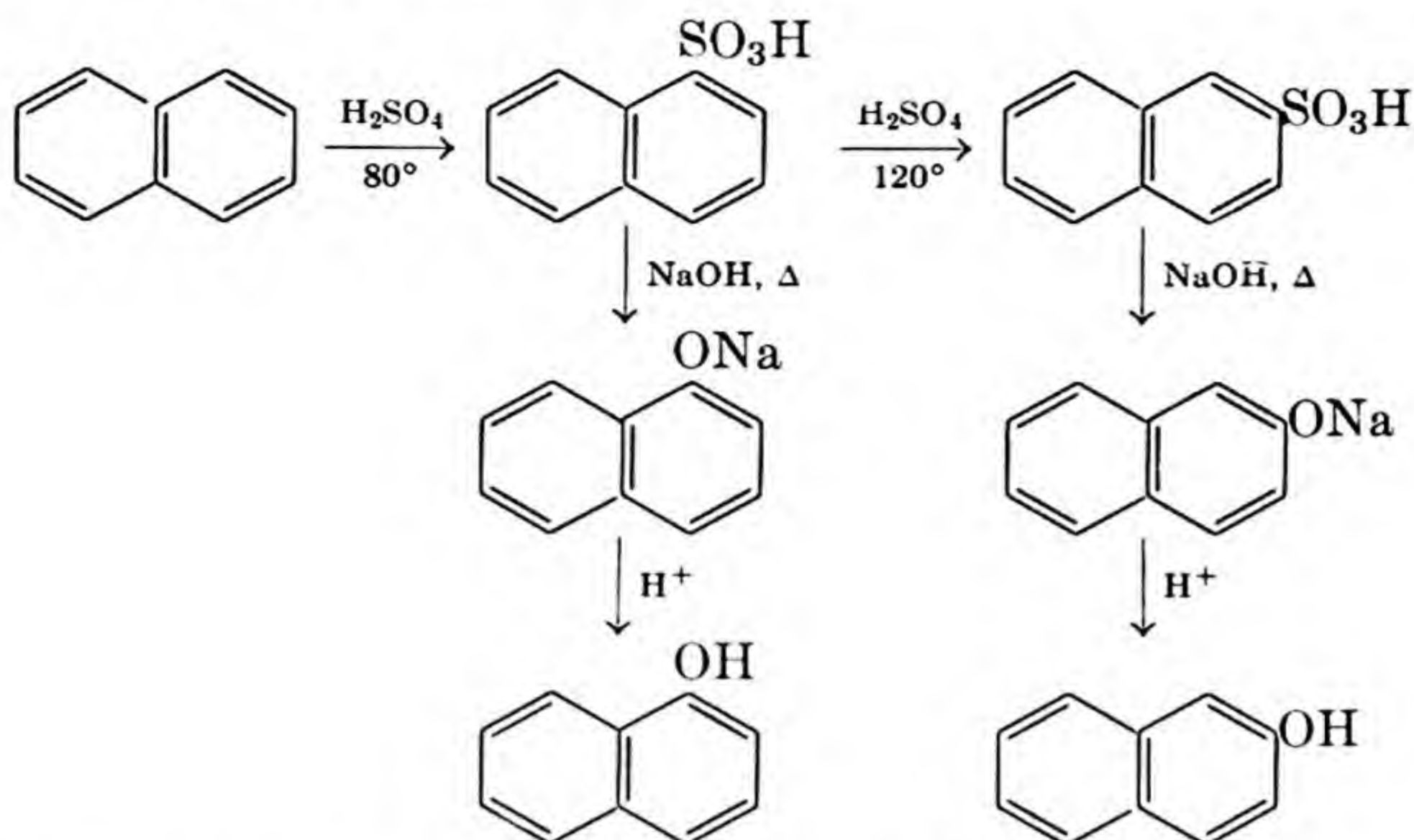
## ► OTHER MONOHYDRIC PHENOLS

The phenols derived from toluene are called cresols, those from naphthalene, naphthols.

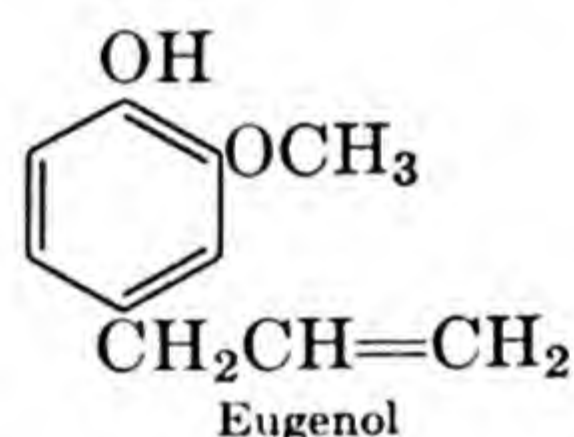
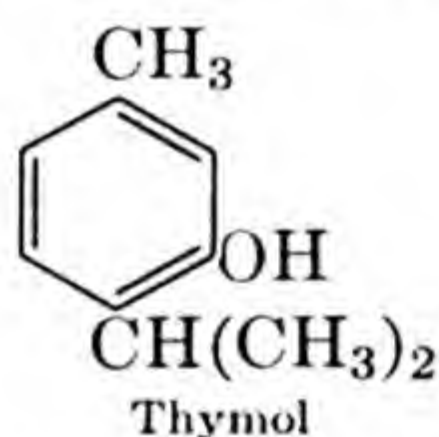


A mixture of the three cresols obtained from the distillation of coal tar is used as a disinfectant. The naphthols and *p*-cresol are obtained by sulfonation, followed by alkali fusion. The naphthols are important dye intermediates.

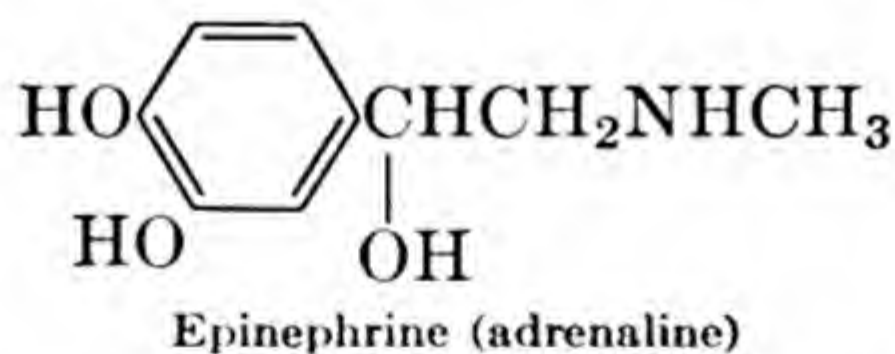




Numerous phenols are found in coal tar. Phenol, all of the cresols, the xylenols (dimethylphenols), and  $\alpha$ - and  $\beta$ -naphthol are examples. Certain plant oils also contain phenols or their derivatives. Thymol occurs in the oil of thyme, anethole in anise and fennel, and eugenol in clove, bay, and cinnamon.



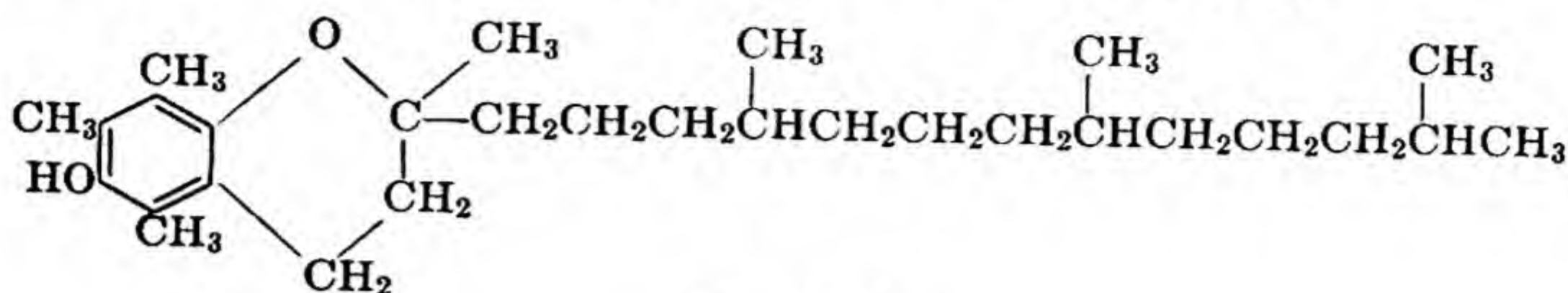
Epinephrine, a hormone produced by the adrenal glands, is at once a phenol, a secondary alcohol, and a secondary amine. When injected into the body it causes constriction of the blood vessels and a stimulation of the heart beat, which result in an increase in blood pressure. Epinephrine also increases the rate of conversion of glyco-



gen into glucose by the body. The natural material is the *l*-isomer; it is about fifteen times as effective as the *d*-compound.

The vitamins E are phenols of complex structure. Rats require vitamin E for normal reproduction. Avitaminosis in other animals leads to other symptoms, often involving the muscles or circulatory system. There is no absolute proof that the vitamin is required in the diet of man, though it is considered essential by authorities. The

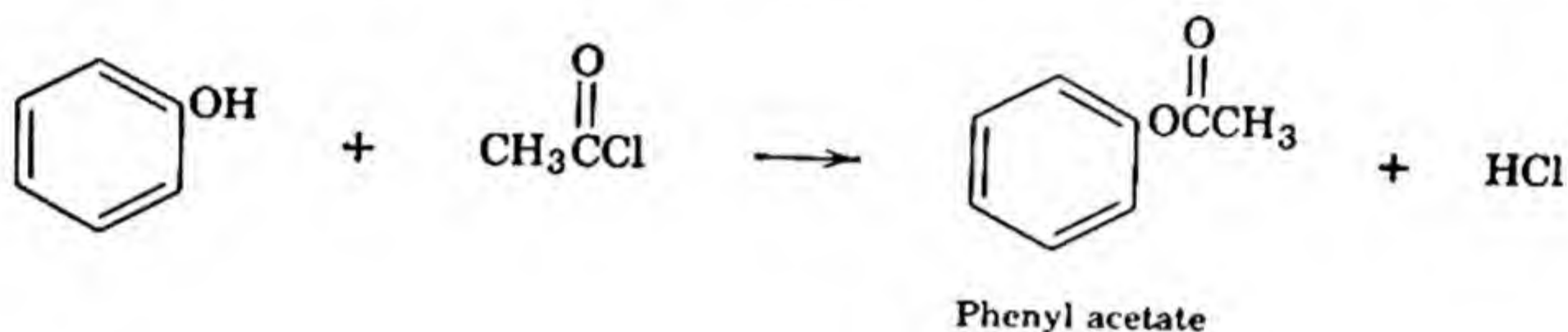
substances with vitamin E activity are known as tocopherols. The most potent is  $\alpha$ -tocopherol; the others ( $\beta$ ,  $\gamma$ ,  $\delta$ ) differ in the number and location of the methyl groups on the benzene ring.



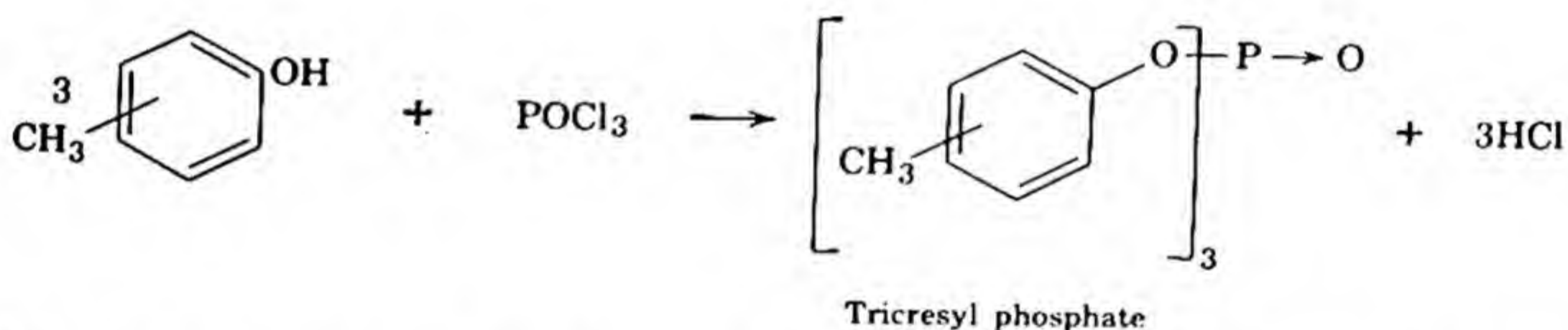
$\alpha$ -Tocopherol

## ► PROPERTIES OF PHENOLS

Most phenols give colors (usually red or purple) with ferric chloride; this fact is used as a test for these compounds. Though phenols do not readily undergo direct esterification with acids, they do react

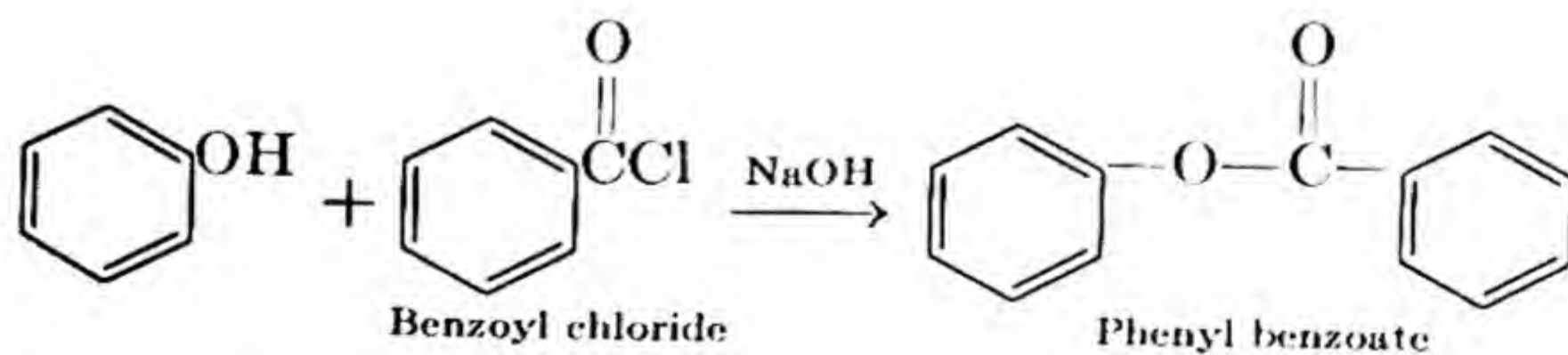


Phenyl acetate



Tricresyl phosphate

with acid chlorides. A mixture of tricresyl phosphates is used as a plasticizer for plastics and as an additive in gasoline. Because of the lesser reactivity of aromatic acid chlorides such as benzoyl chloride it is desirable to use an alkali with the other reactants. Such a procedure is known as the *Schotten-Baumann* method.



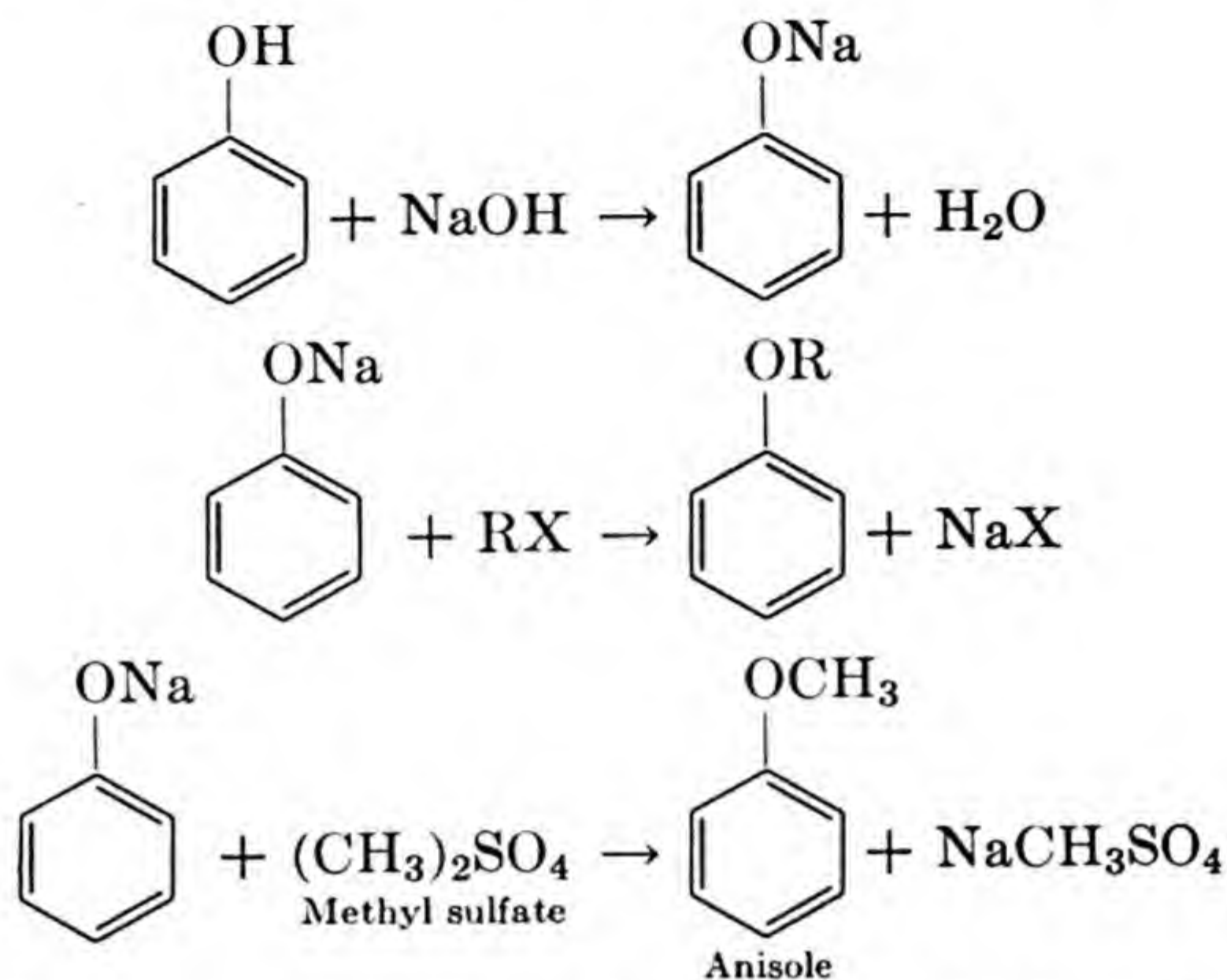
Benzoyl chloride

Phenyl benzoate

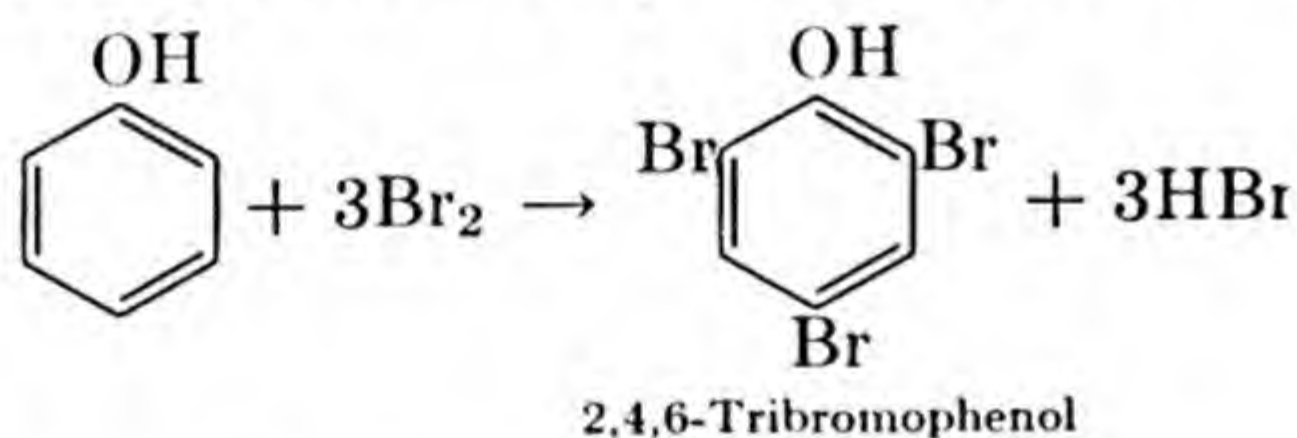
The phenols can be made to form ethers by a type of Williamson synthesis (Chapter 8). Ordinarily, the phenol is shaken with aque-



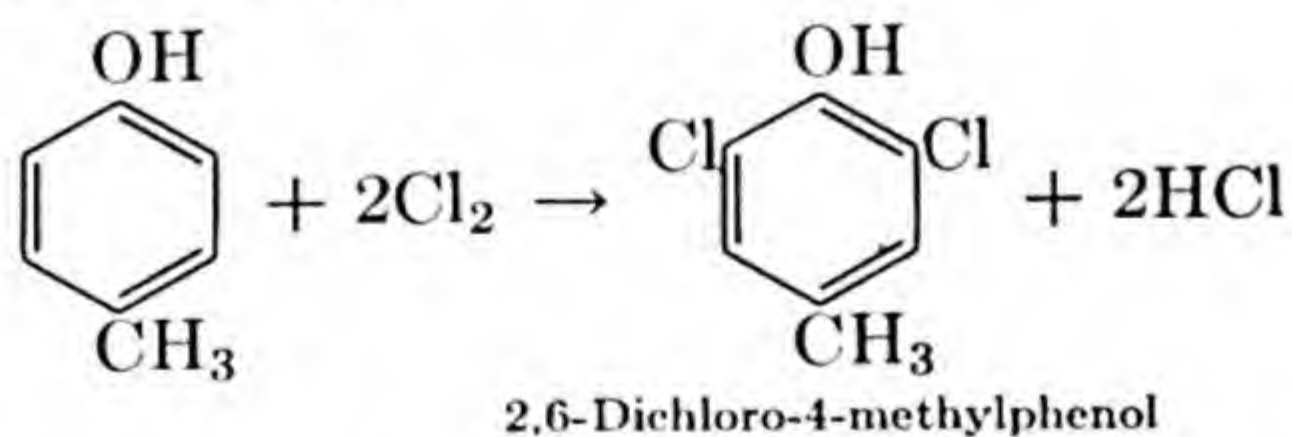
ous sodium hydroxide and an alkyl halide or sulfate at room temperature.



The hydrogen atoms *ortho* and *para* to the hydroxyl group in phenols are extremely reactive. Thus phenols couple with diazonium salts (Chapter 14) and are easily halogenated. Phenol readily undergoes tribromination at room temperature by bromine water.

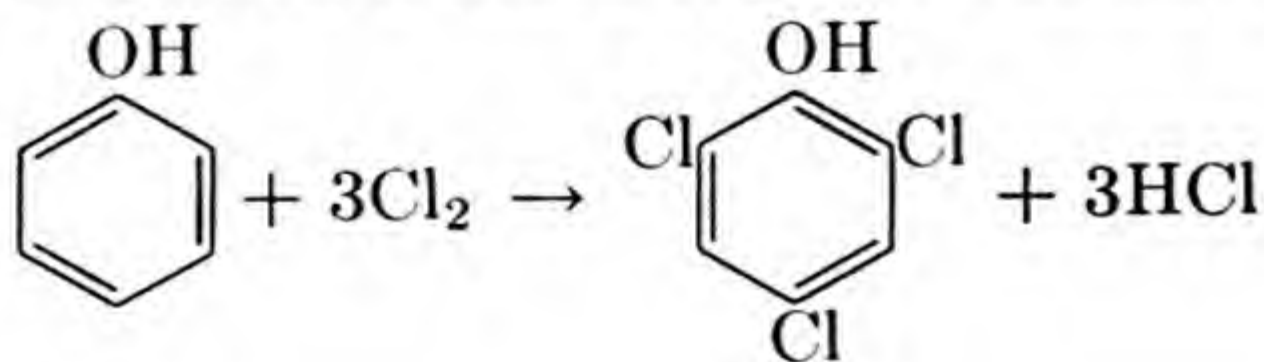


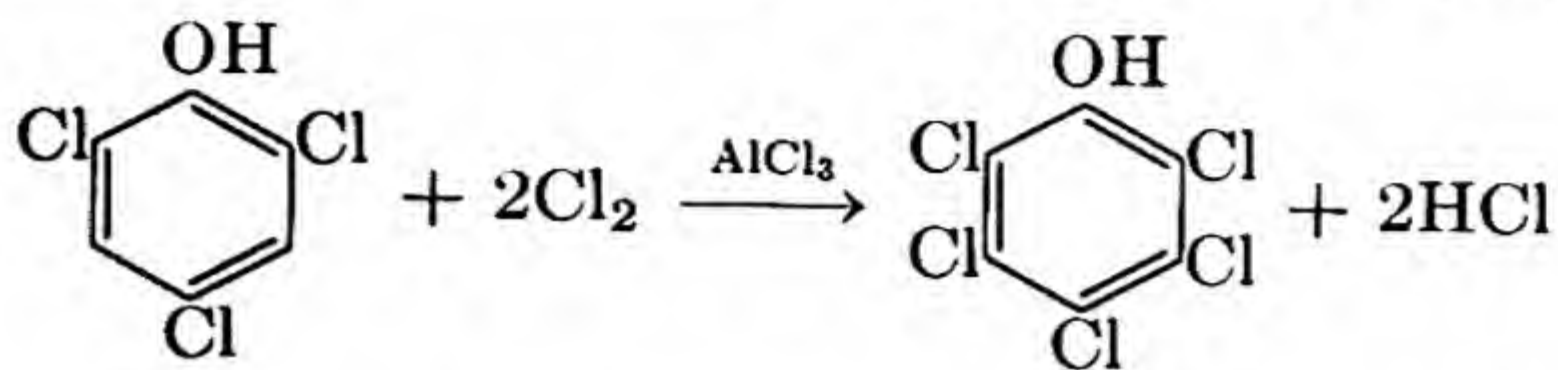
Chlorine also attacks phenols.



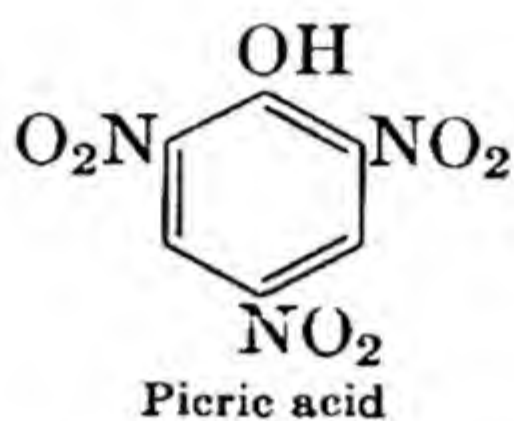
The complete chlorination of phenol yields pentachlorophenol, a compound useful as a fungicide and particularly as a wood preservative.

The chlorination to the trichloro stage occurs readily, but introduction of the final two chlorine atoms requires a catalyst.



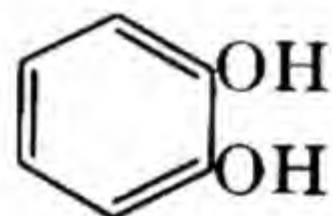


The nitration of phenol produces 2,4,6-trinitrophenol, usually known as picric acid, though it is better made by nitration of chlorobenzene and hydrolysis. Picric acid, a yellow substance, is a high explosive, and it is curious that it is employed also in the treatment of burns. Like all phenols, it has an anesthetic action on the skin.

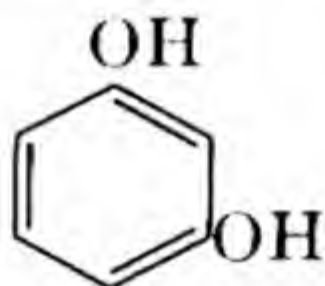


## ► POLYHYDRIC PHENOLS

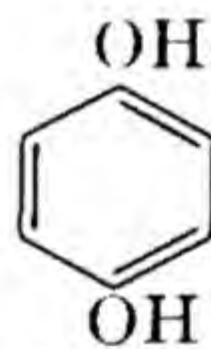
The three dihydroxybenzenes are commercial products. Catechol



Catechol

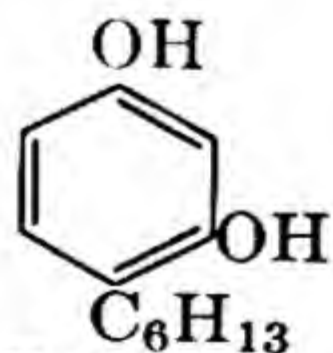


Resorcinol

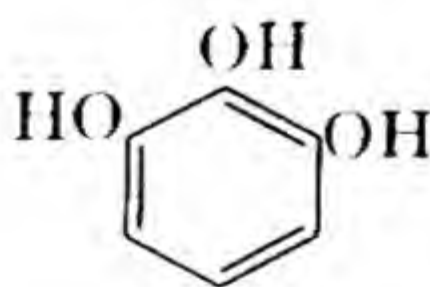


Hydroquinone

finds use in the manufacture of antioxidants such as *t*-butylcatechol. Resorcinol has germicidal properties similar to those of phenol and is an ingredient of hair tonics. Hexylresorcinol, a derivative made from resorcinol, is used as a mouthwash and gargle. Hydroquinone in alkaline solution is a good reducing agent and serves as a photographic developer. The trihydroxybenzene, pyrogallol, is very easily oxidized; an alkaline solution of it is efficient in removing traces of oxygen from gases.



Hexylresorcinol

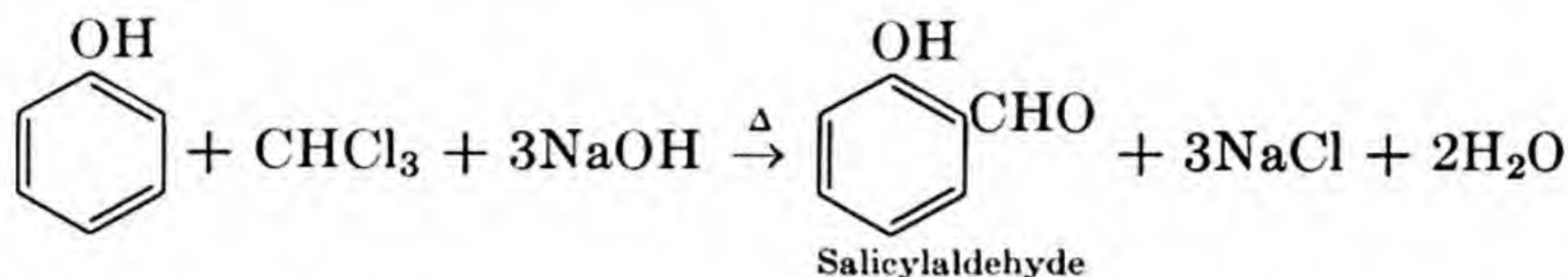


Pyrogallol



## ► PHENOLIC ALDEHYDES

Certain phenolic aldehydes can be prepared by the Reimer-Tiemann reaction which requires a phenol, chloroform, and an alkali. With phenol itself, there results a mixture of *o*- and *p*-hydroxybenzaldehydes, with the former (usually known as salicylaldehyde) predominating.

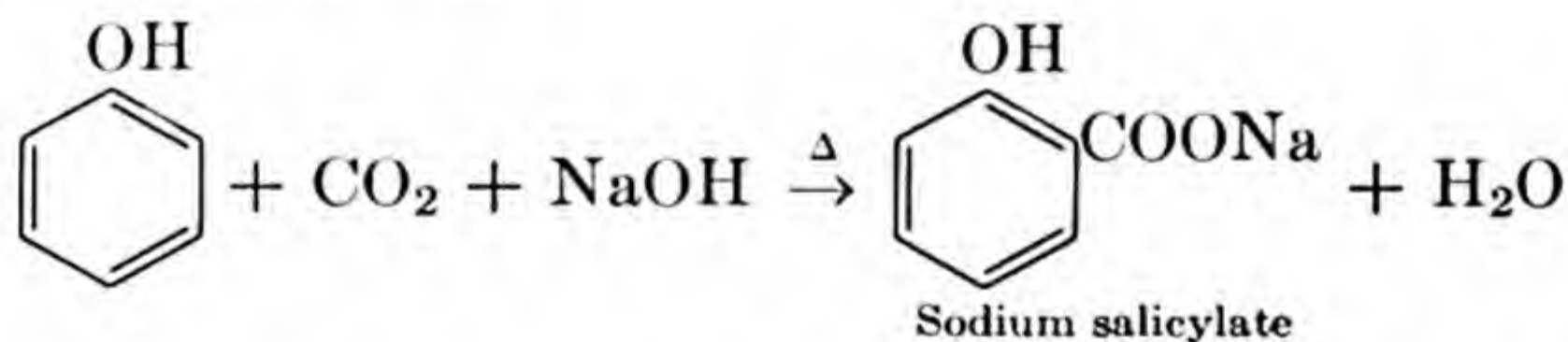


Vanillin, the chief constituent of extract of vanilla, is a phenolic aldehyde. It can be prepared by a Reimer-Tiemann reaction with guaiacol and is also obtained in the hydrolysis of lignin.



## ► PHENOLIC ACIDS

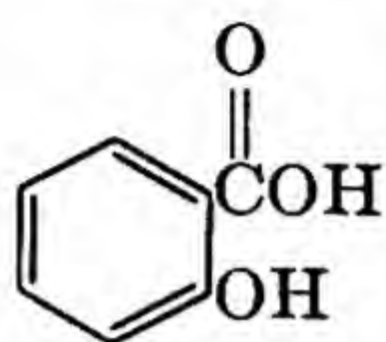
When phenol is heated with sodium hydroxide and carbon dioxide, sodium salicylate results.



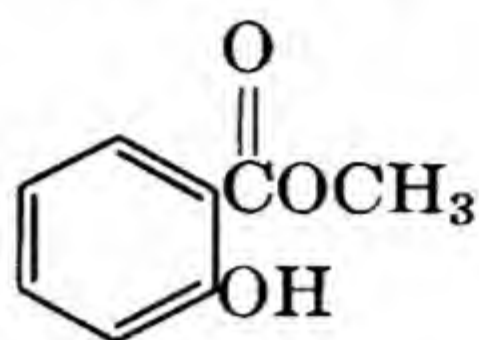
Salicylic acid, which is produced from sodium salicylate upon acidification, is at once an acid and a phenol. It is used as an antiseptic, in the preservation of wines and food, and in the preparation of important medicinals. Salol, the phenyl ester of salicylic acid, passes unchanged through the stomach. It is hydrolyzed in the intestine to salicylic acid and phenol and is therefore a very effective intestinal antiseptic, though it has been partially supplanted by certain sulfa drugs. Aspirin, widely employed to counter the unpleasant effects of colds, grippe, neuralgia, and headaches and to reduce fevers, is the acetyl derivative of salicylic acid. The methyl ester of salicylic acid



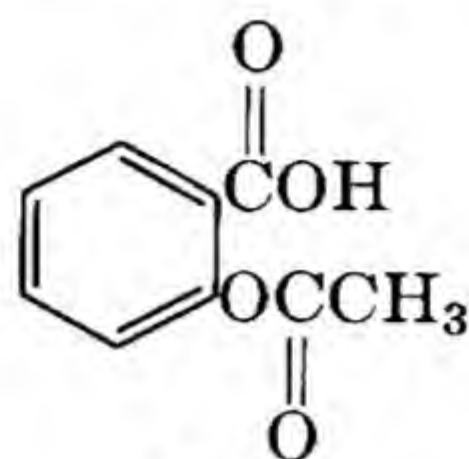
is known as oil of wintergreen and is contained in certain remedies for aches and sprains; it penetrates the skin and then undergoes hydrolysis to salicylic acid, which relieves the local pain.



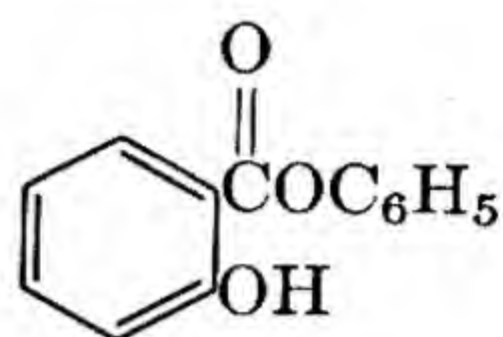
Salicylic acid



Methyl salicylate



Aspirin

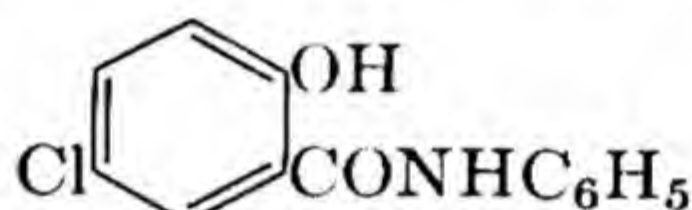


Salol

Salicylic acid and some of its derivatives, such as salicylanilide and 5-chlorosalicylanilide, are employed in the treatment of fungus diseases of the skin (athlete's foot and ringworm of the scalp, which sometimes occurs epidemically among school children). *p*-Amino-



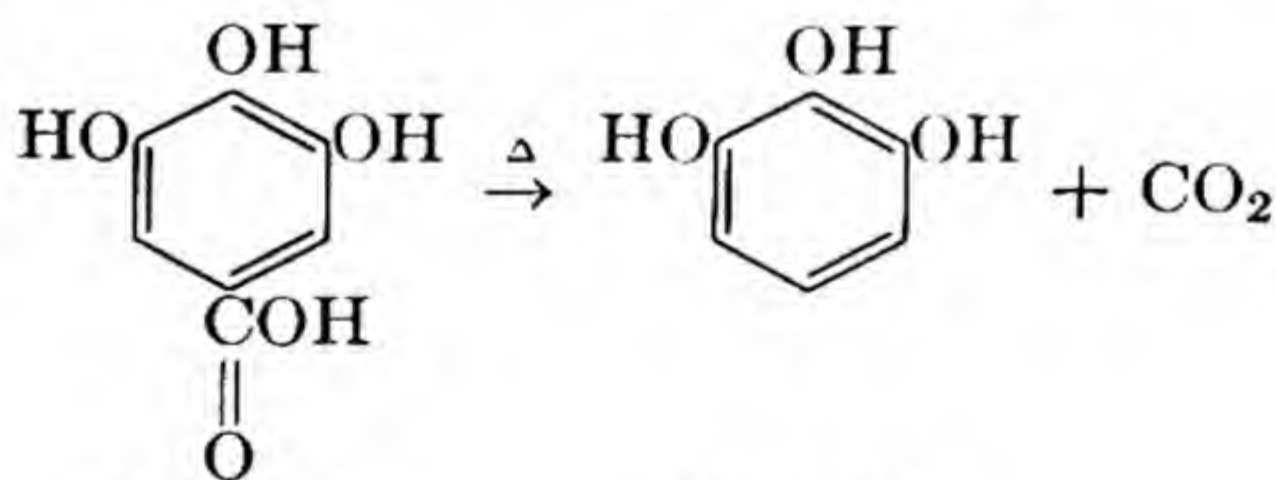
Salicylanilide



5-Chlorosalicylanilide

salicylic acid (PAS) is an important medication in the treatment of tuberculosis. It is helpful when administered in conjunction with streptomycin because it delays the emergence of strains resistant to that antibiotic.

Gallic acid (3,4,5-trihydroxybenzoic acid) is obtained in the hydrolysis of tannic acid. It finds use in tanning leather and in the compounding of inks and dyes. In medicine it is employed as an astringent and in the treatment of burns. Gallic acid esters are incorporated as antioxidants into foods such as lard. The decarboxylation of gallic acid is a method of preparing pyrogallol.



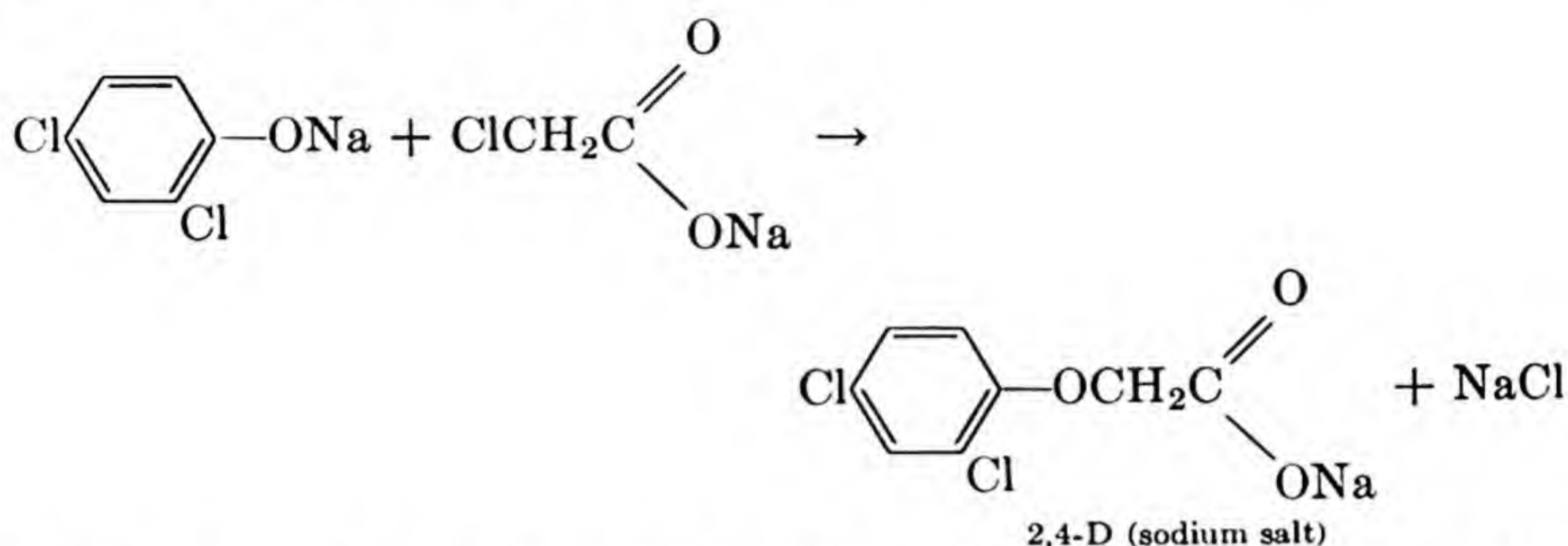
Gallic acid

Pyrogallol

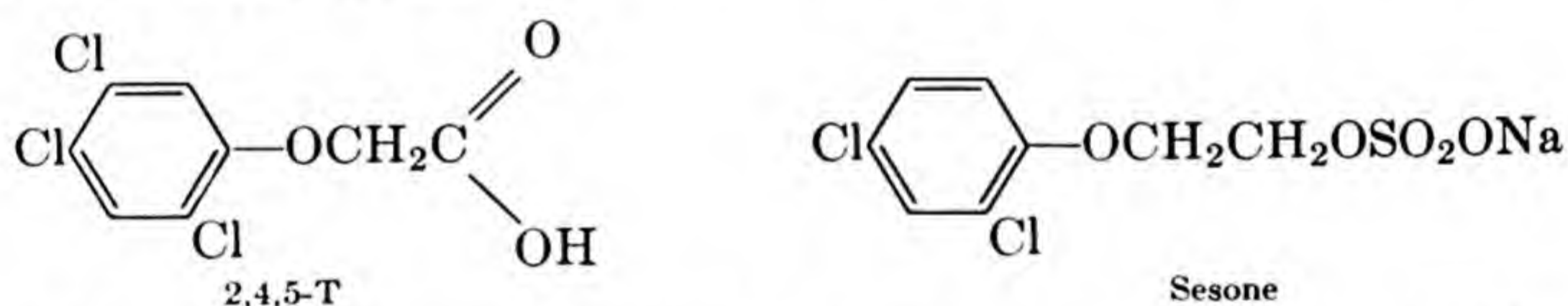
Certain chlorinated phenols have found employment in the preparation of herbicides, used to kill undesirable plant growth. Probably the best-known organic herbicide is 2,4-D (2,4-dichlorophenoxyacetic acid). It is highly toxic to most broad-leaved plants but less so to cereals and grasses and therefore is applied to grain fields and



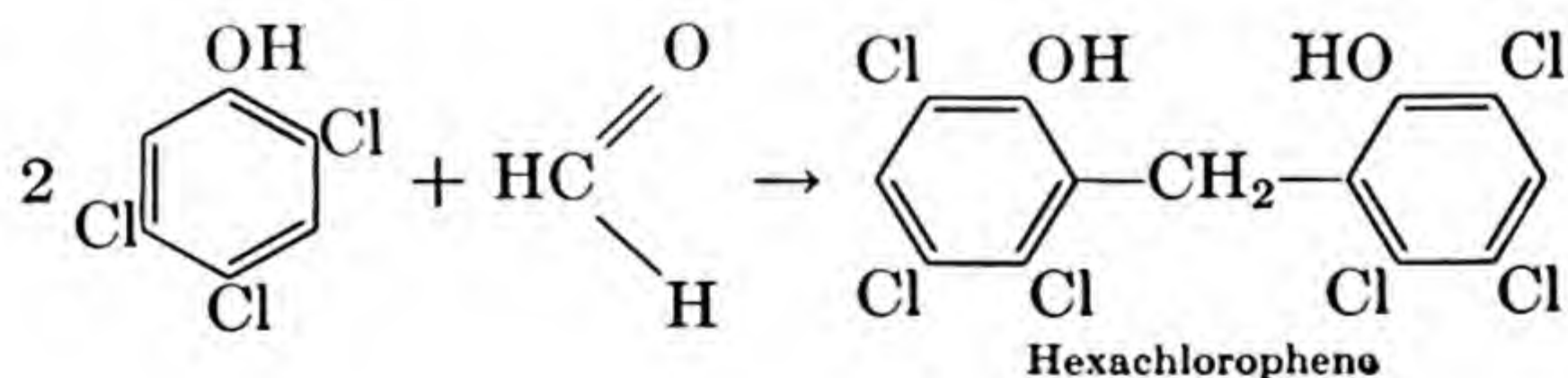
pastures. It is synthesized from chloroacetic acid and 2,4-dichlorophenol in the presence of alkali.



Various esters and salts of 2,4-dichlorophenoxyacetic acid are also employed as herbicides. 2,4,5-Trichlorophenoxyacetic acid (2,4,5-T) and its derivatives are similarly useful but are more destructive to woody plants. It is believed that the efficacy of 2,4-D and 2,4,5-T is connected with their similarity in structure to some of the plant hormones. These herbicides are absorbed by the leaves and stem of the plant and are translocated to the roots. When their esters or salts are employed hydrolysis occurs and the free acids, which are the active compounds, result. An herbicide related to 2,4-D is sodium 2,4-dichlorophenoxyethyl sulfate (Sesone) which is effective for strawberry and corn crops and as a pre-emergence spray for lawns to control crab grass.



2,4,5-Trichlorophenol reacts with formaldehyde to give hexachlorophene, which has application as a skin disinfectant. On this account it is incorporated into soaps, shaving creams, face creams, and the like.

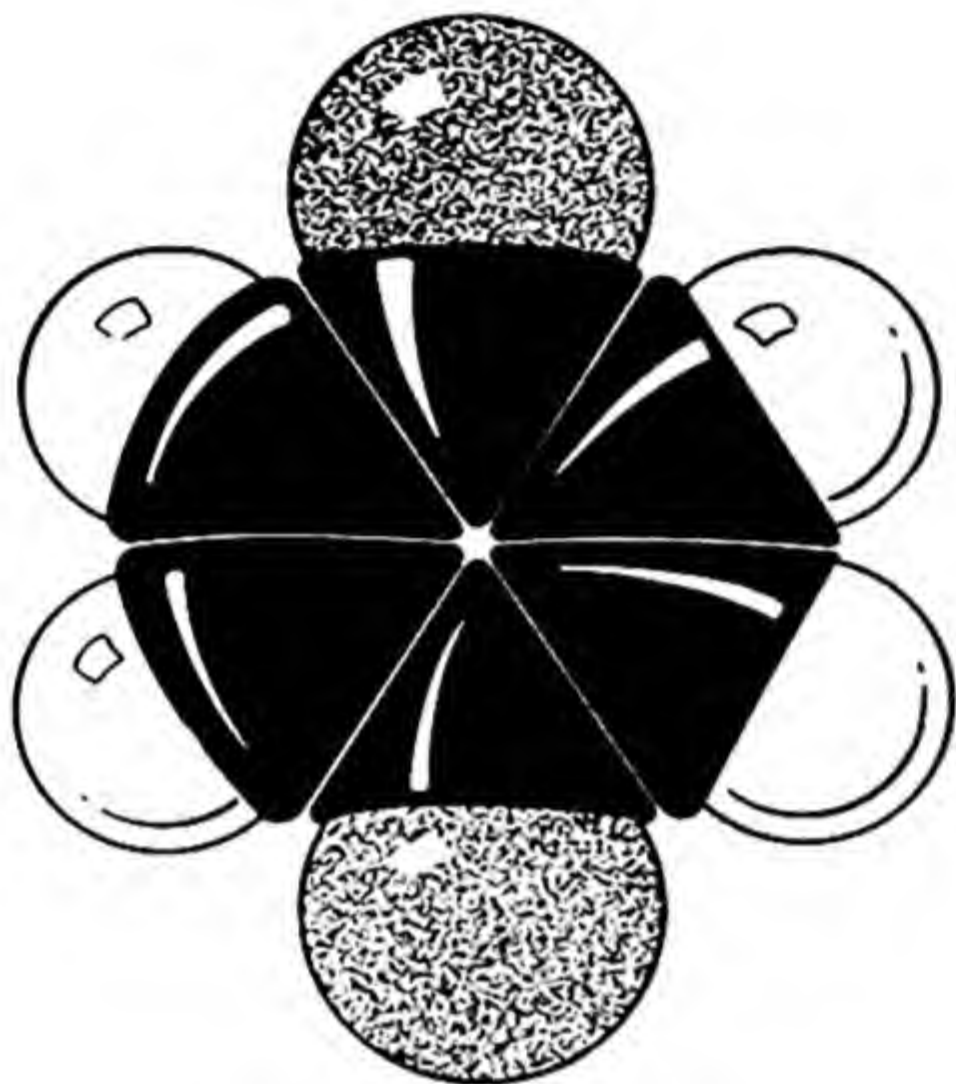


## ► QUESTIONS

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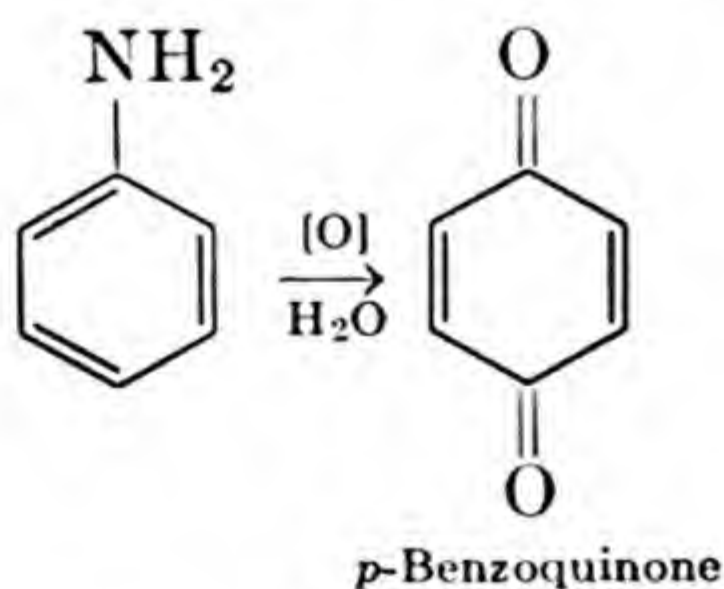
1. Write equations for the following reactions:
  - (a) *o*-Cresol + bromine (excess) →
  - (b) Hydroquinone + acetyl chloride →
  - (c)  $\alpha$ -Naphthol + benzoyl chloride + sodium hydroxide →
2. Write equations to show how boiling aqueous sodium hydroxide would react with (a) aspirin; (b) salol.
3. Describe a procedure suitable for the separation of methyl salicylate and aspirin.



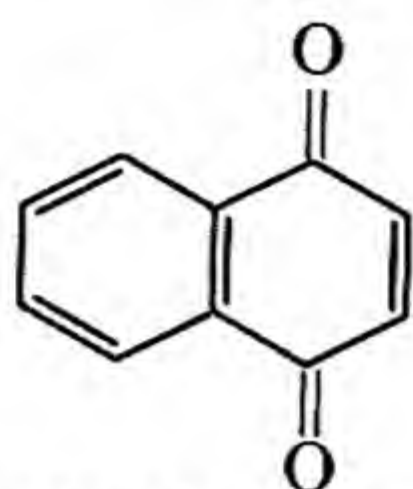


Though it is easily obtained by the oxidation of hydroquinone, an aromatic compound, quinone itself is nonaromatic.

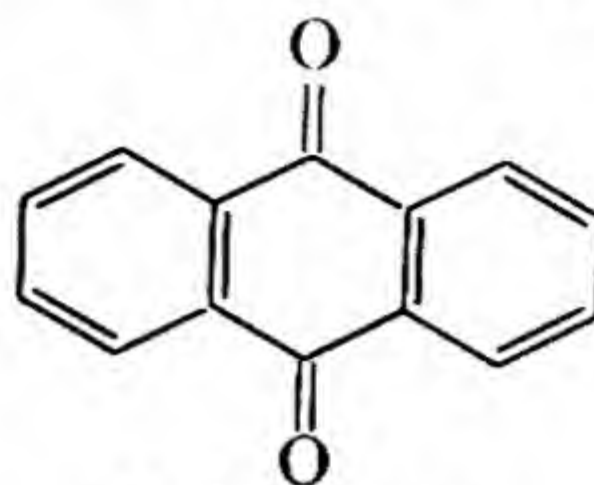
The oxidation of aniline with chromic acid brings about a very peculiar reaction involving the loss of the aromatic character of the ring. The product is known as *p*-benzoquinone.



Other common quinones are 1,4-naphthoquinone and anthraquinone.



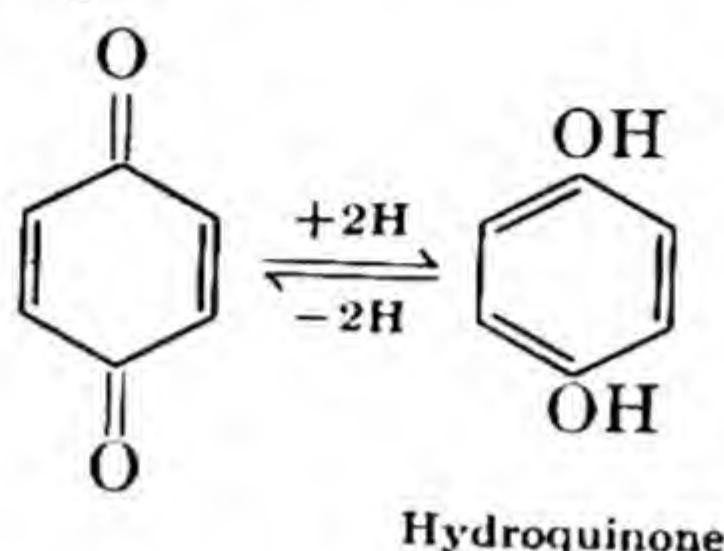
1,4-Naphthoquinone



Anthraquinone

The quinones are colored compounds, and many synthetic dyes belong to this class of substance. Quinones also occur as the pigments in certain plants, molds, and fungi. The vitamins K are derivatives of 1,4-naphthoquinone.

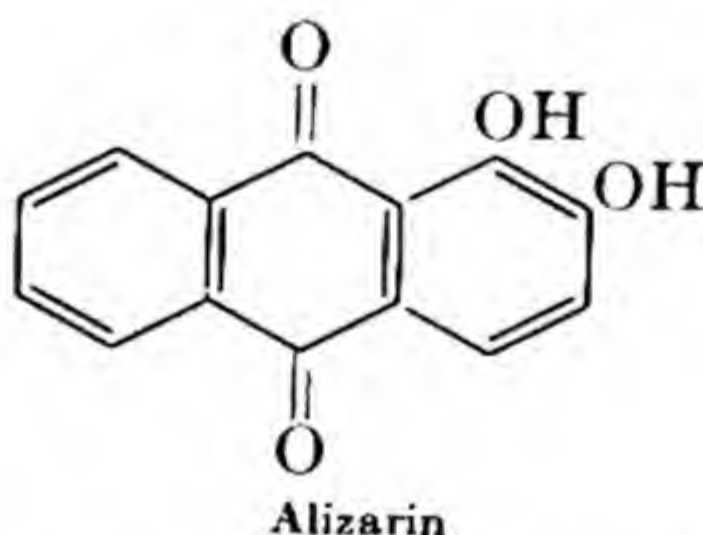
Quinones are readily reduced to hydroquinones; the reverse reaction also occurs very easily.



Hydroquinone

## ► ANTHRAQUINONE DYES

Certain derivatives of anthraquinone are valuable dyes. The most important is alizarin, known for centuries and previously obtained from the madder plant but now made synthetically from anthraquinone.



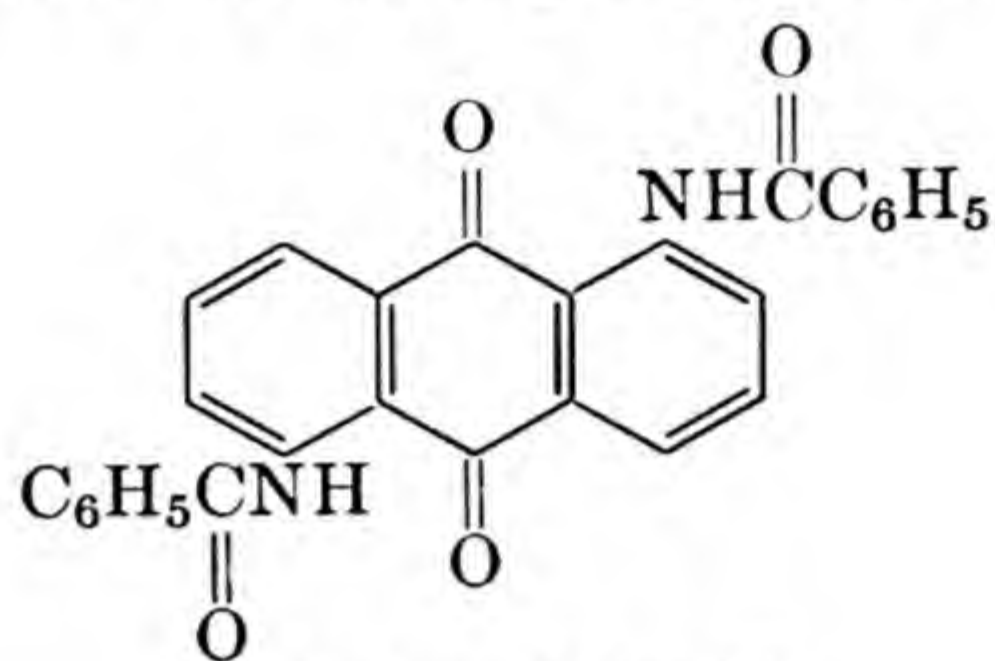
Alizarin

Dyes of this type are very frequently employed in connection with certain metallic hydroxides called *mordants* with which they react to form brilliantly colored compounds, or *lakes*. The color of the lake varies with the hydroxide. Alizarin, for example, gives a red dye with aluminum salts, a violet dye with an iron mordant, and brownish red with chromium. The most important use of alizarin is in dyeing cotton a bright hue known as Turkey red.

Some anthraquinone dyes are applied by a process known as *vat dyeing* which takes advantage of the easy reduction of quinones to



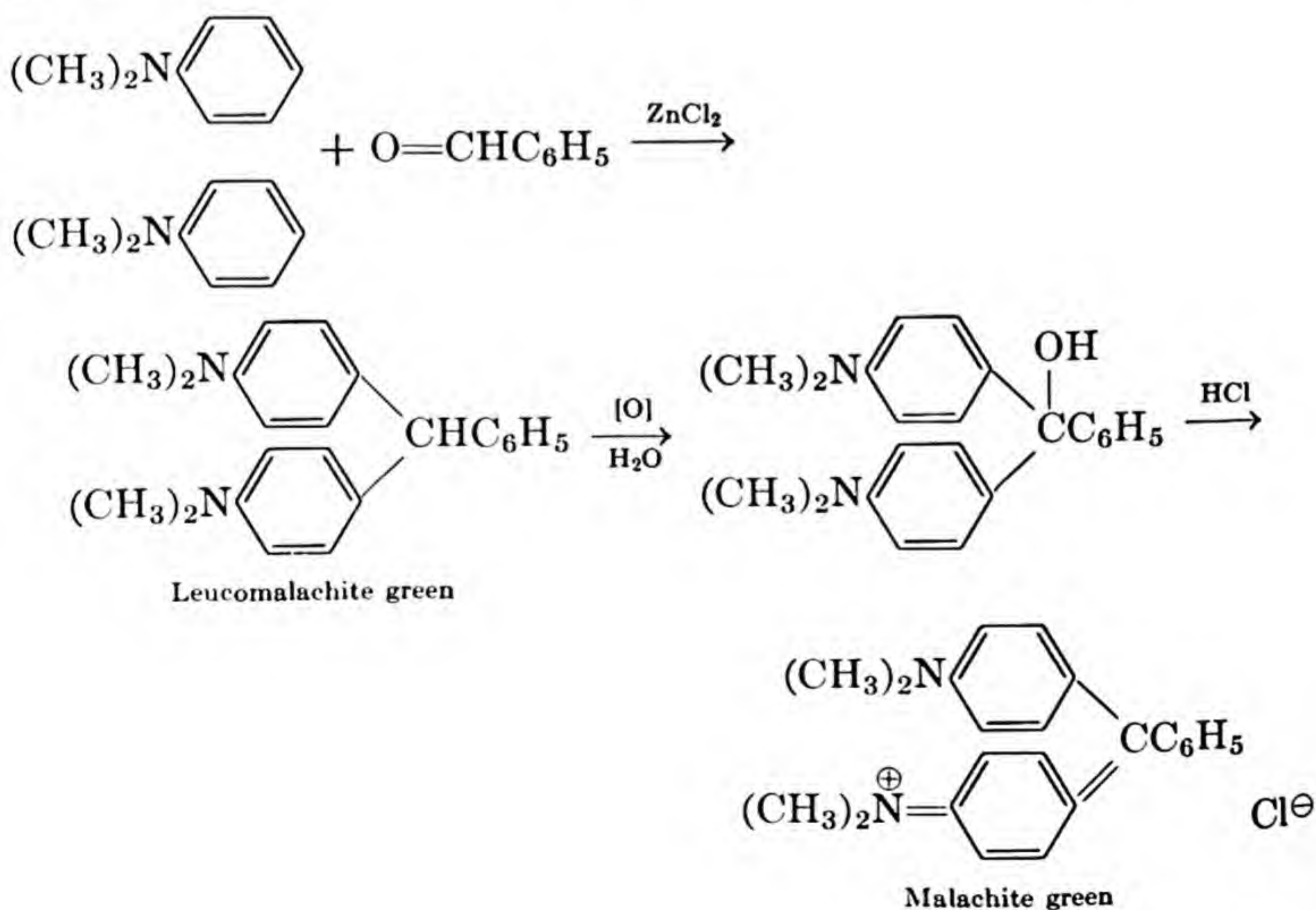
hydroquinones. The quinones are usually insoluble in water, whereas the hydroquinones are soluble. In the vat dyeing process the cloth is soaked in a solution of the reduced dye (hydroquinone); it is then removed from the bath and allowed to undergo oxidation in the air or is treated with a chemical oxidizing agent. The quinone is thus regenerated. An example of a dye of this type is Indanthrene Yellow GK, but most of the vat dyes currently in use are of much more complex structure. Vat-dyeing is particularly useful for cotton.



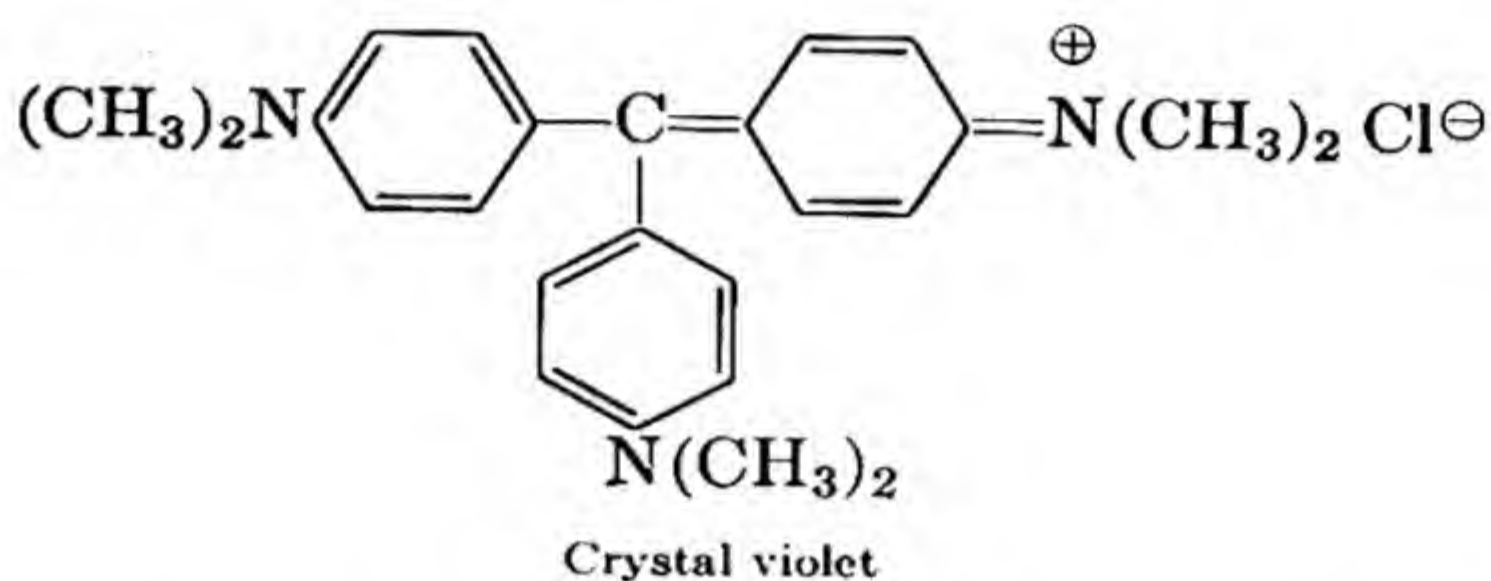
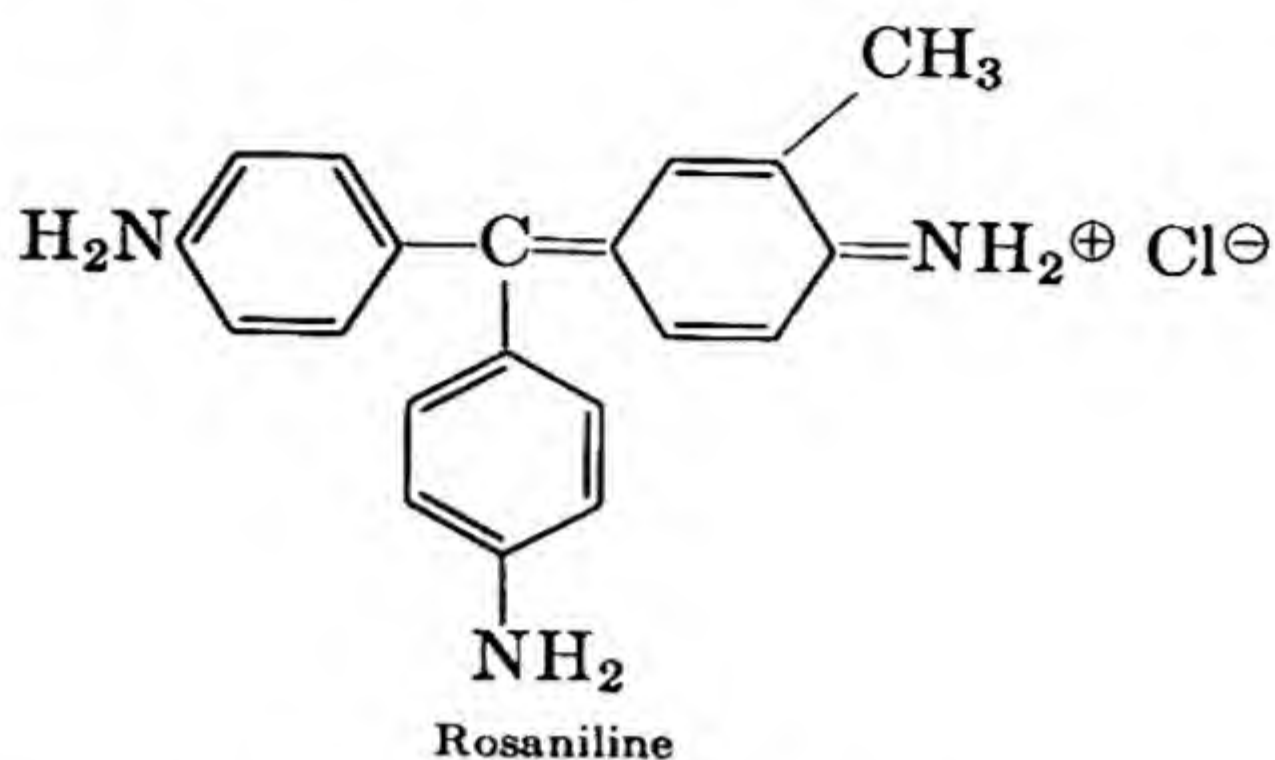
Indanthrene Yellow GK

### ► TRIPHENYLMETHANE DYES

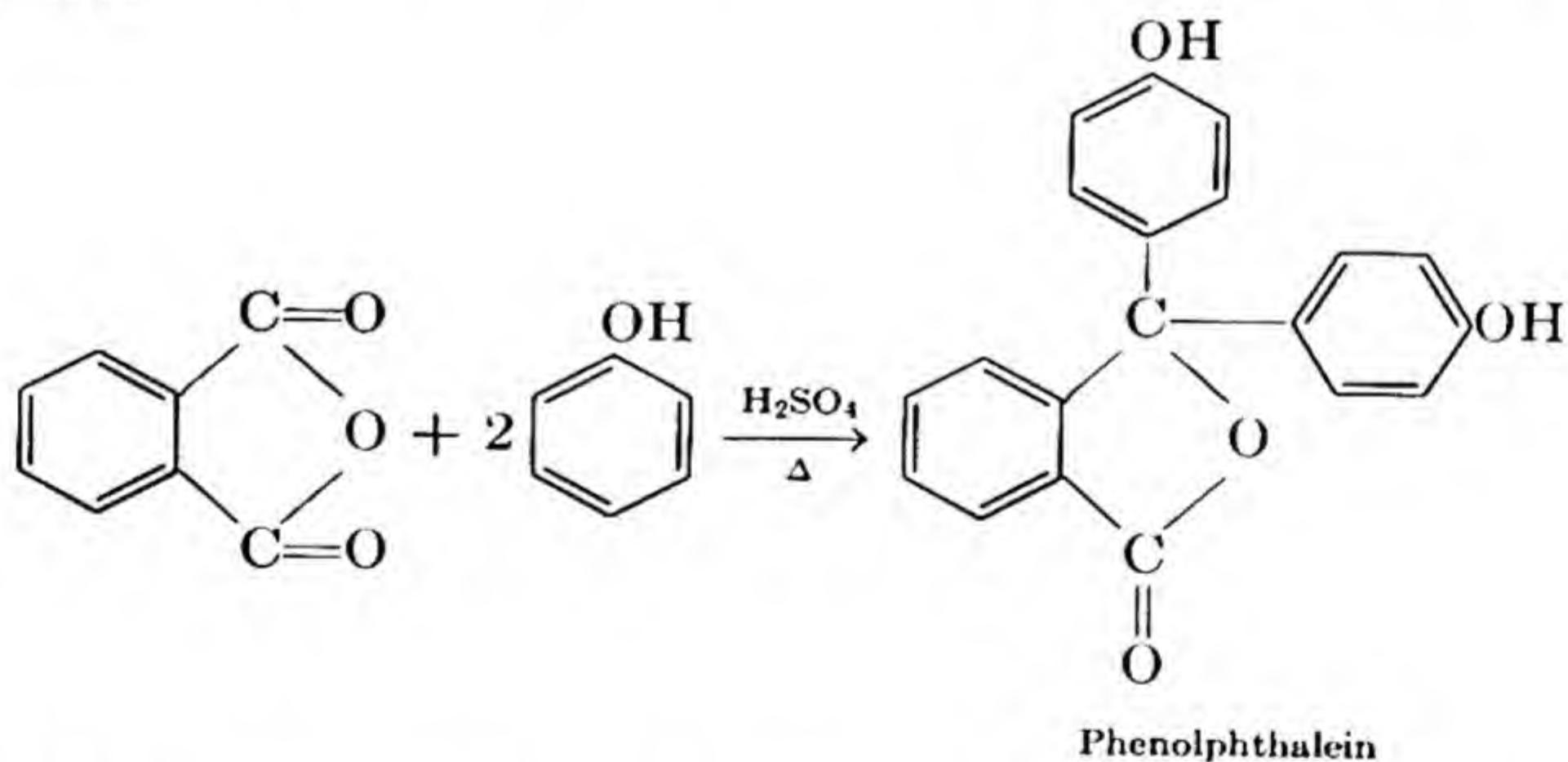
Certain derivatives of triphenylmethane pass into a quinone type of structure upon oxidation in an acid medium. In this way the so-called triphenylmethane dyes are produced. An example is malachite green.



Other examples of triphenylmethane dyes are rosaniline and crystal violet.

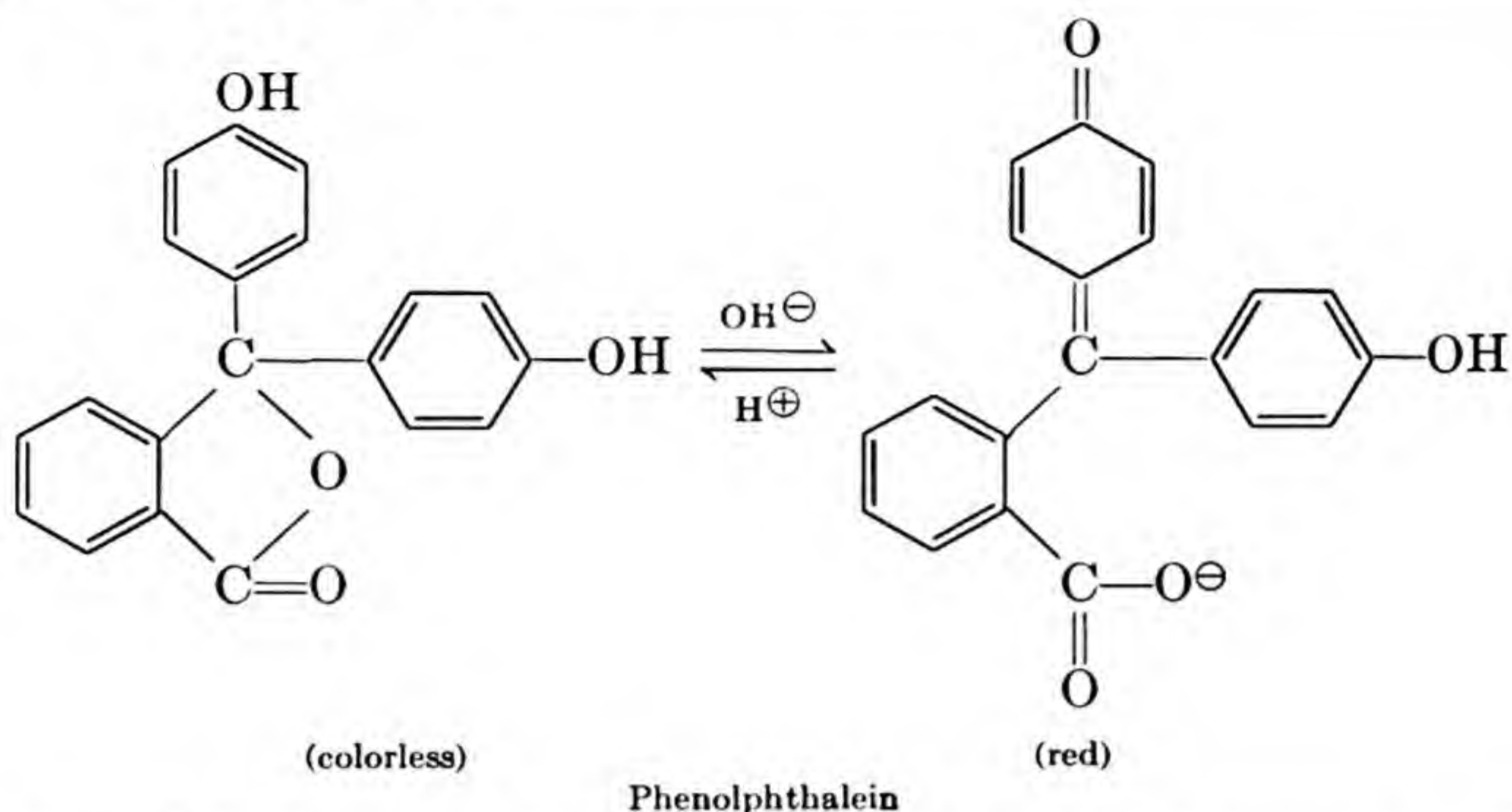


The phthaleins are also triphenylmethane derivatives. The simplest of these, phenolphthalein, can be prepared from phenol and phthalic anhydride.

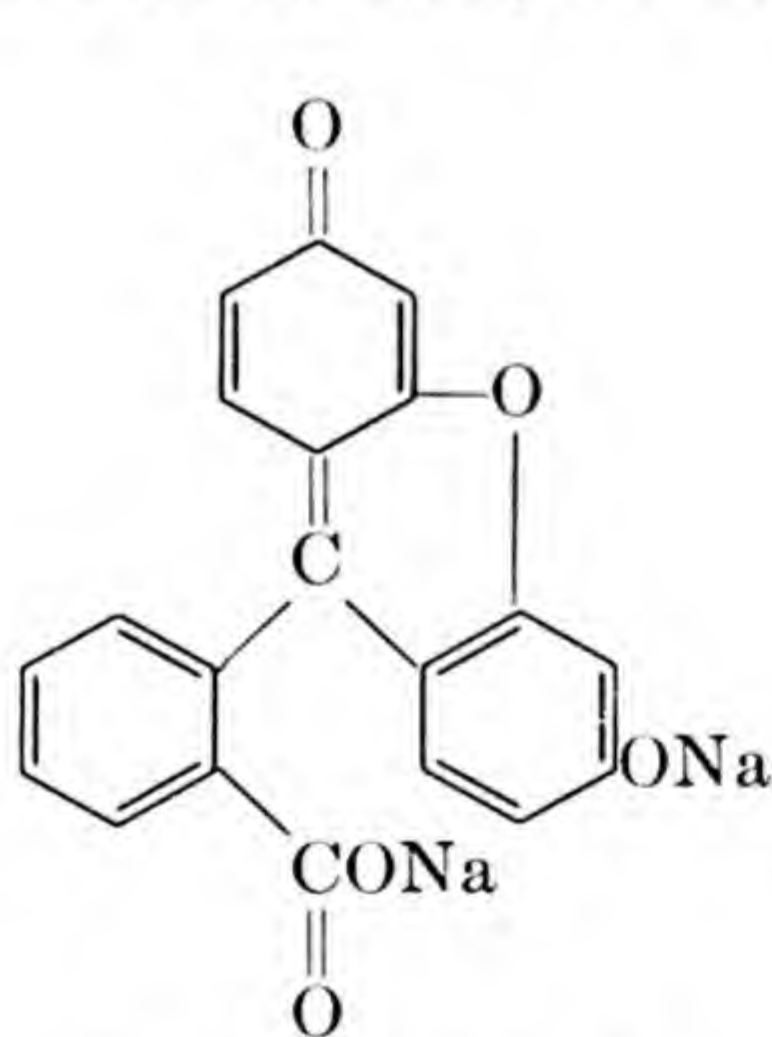


Phenolphthalein is used as a laxative and as an acid-base indicator. The latter application is based upon the fact that treatment of the colorless phenolphthalein with alkali converts it into a red form which contains a quinoid structure. The reaction is reversed by acids.

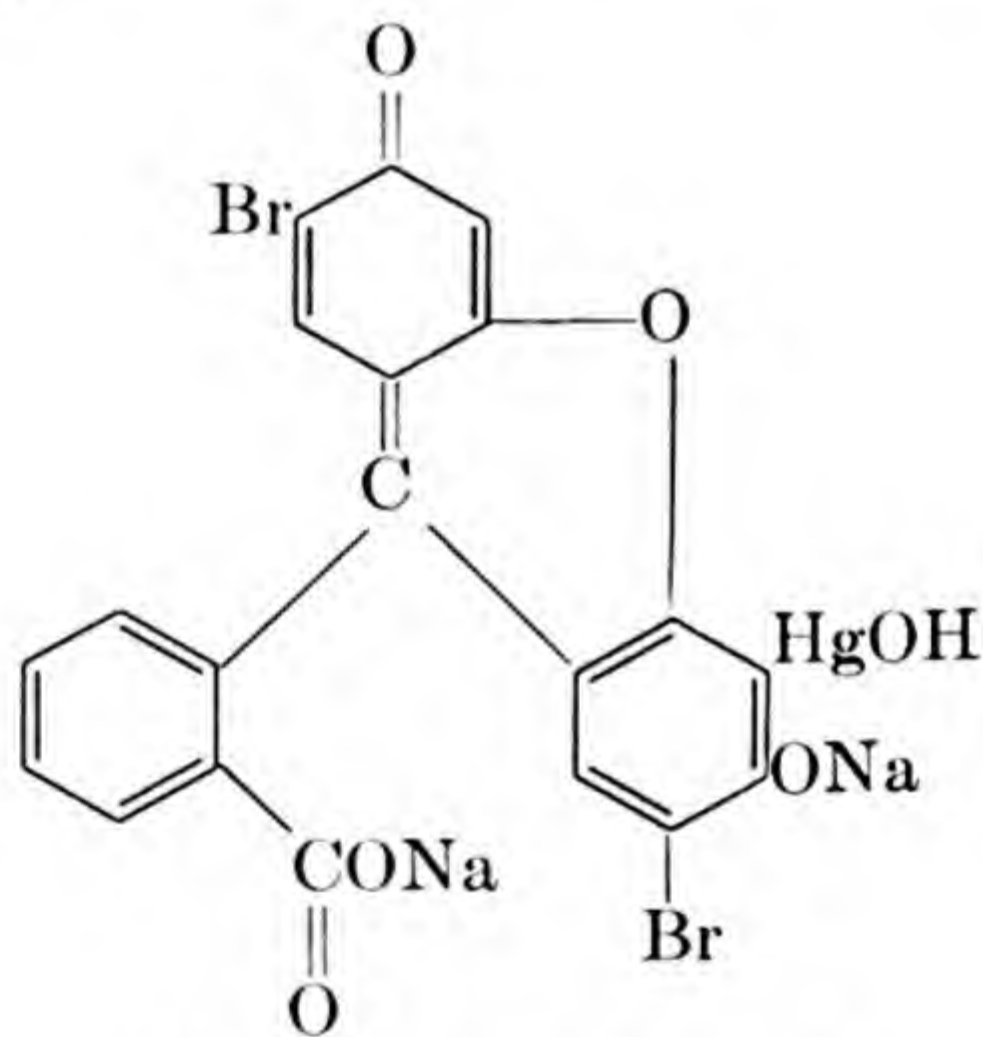




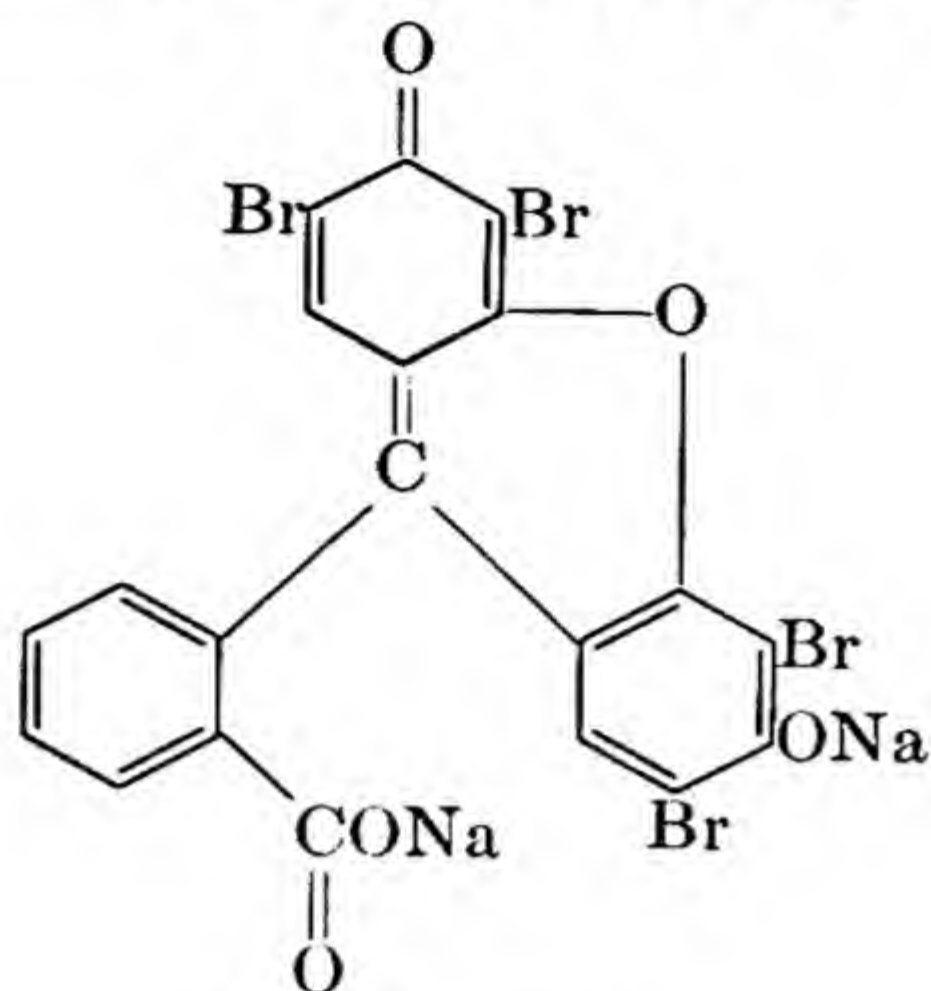
Other phthaleins can be similarly prepared. Fluorescein, one of the most interesting, is made from phthalic anhydride and resorcinol. Fluorescein in the presence of even a small amount of alkali appears yellow by transmitted light and green by reflected light. It is employed in lubricating oils, bath salts, and in other applications in which this appearance is desired. Certain derivatives of fluorescein are also useful; mercurochrome, an antiseptic, and eosin, a component of red inks, are examples.



Fluorescein (sodium salt)



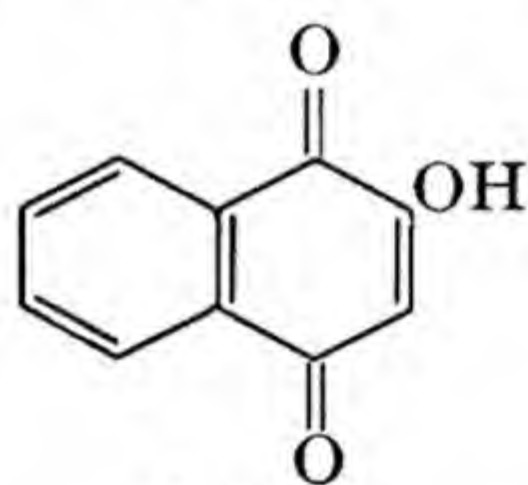
Mercurochrome (sodium salt)



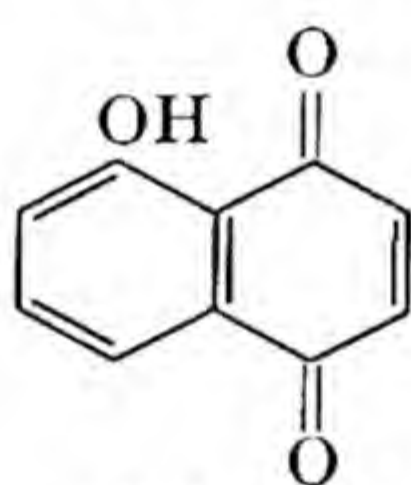
Eosin (sodium salt)

## ► NATURALLY OCCURRING QUINONES

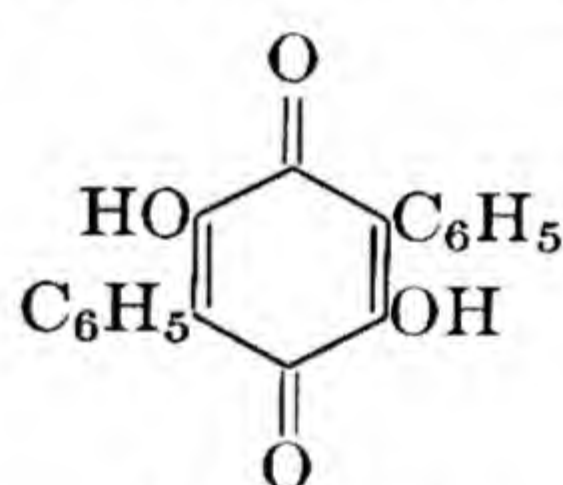
As mentioned previously, certain quinones occur as pigments in molds, fungi, and plants. Lawsone is extracted from the henna plant and has long been used as a dye. Juglone occurs in green walnut shells, and polyporic acid occurs in certain fungi found on oak trees.



Lawsone

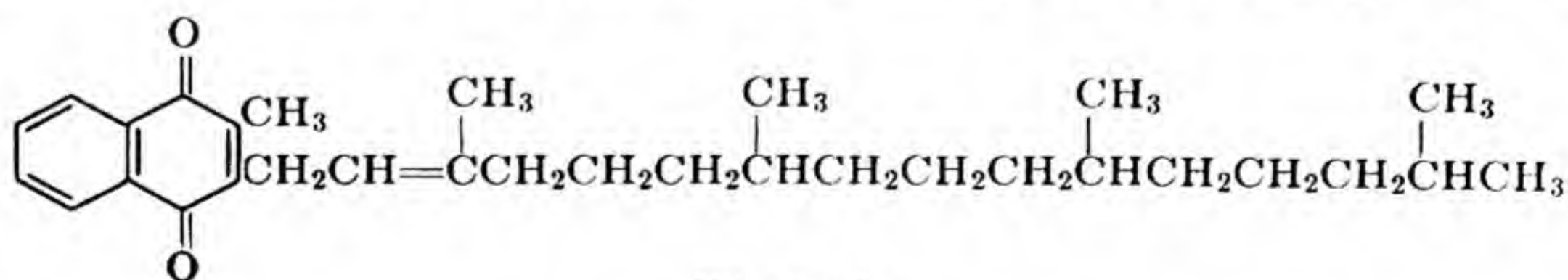


Juglone



Polyporic acid

The most important of the naturally occurring quinones are the vitamins K, which are concerned in the clotting of blood. Numerous synthetic compounds have activity, but only two are known to occur naturally. They are derivatives of 2-methyl-1,4-naphthoquinone and



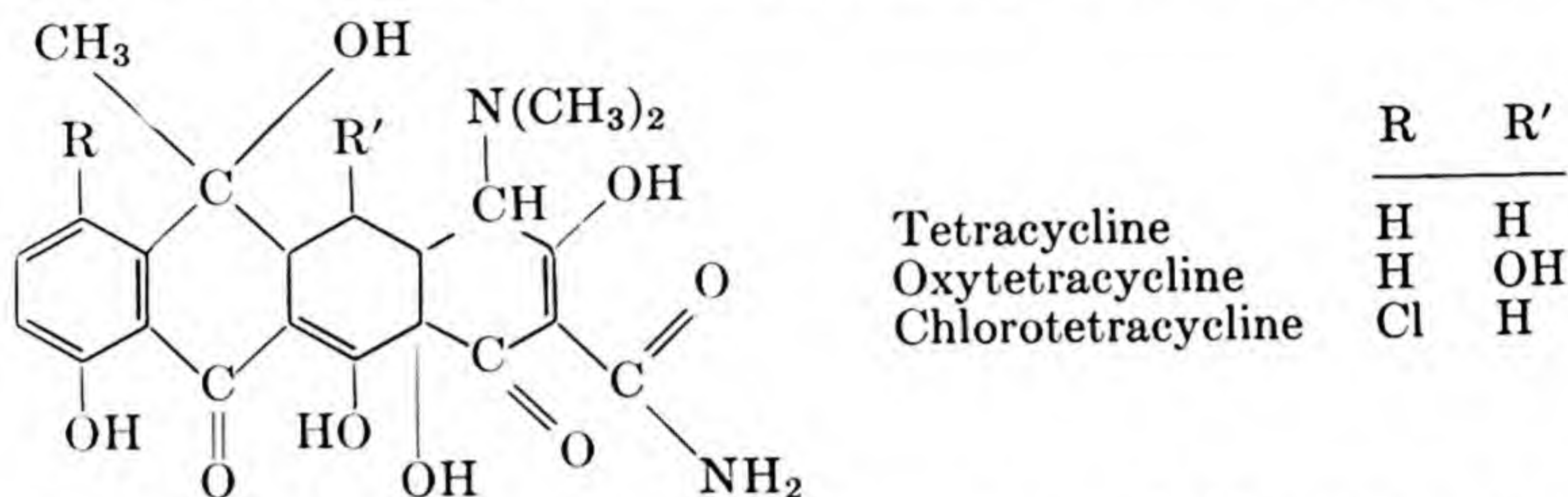
Vitamin K<sub>1</sub>

differ only in the long side chain. In K<sub>1</sub> there is a phytyl group; in K<sub>2</sub>, a difarnesyl group which has thirty carbon atoms and three double bonds. The compound without the side chain, 2-methyl-1,4-naphthoquinone, has vitamin K activity. It is sold under the name



Menadione and is prepared by the oxidation of 2-methylnaphthalene. Hypovitaminosis K occurs very rarely in humans because the vitamin is consumed in the ordinary diet and because intestinal microorganisms are capable of synthesizing K<sub>2</sub>.

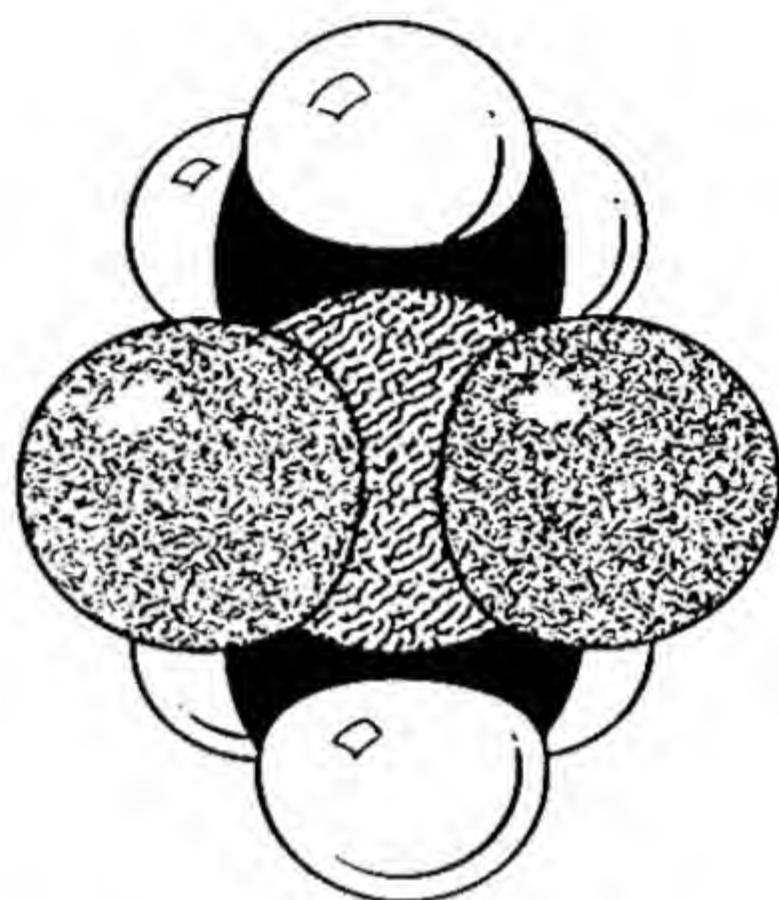
Though they are not quinones, the antibiotics of the tetracycline type are in some degree related structurally to them. Tetracycline



(Achromycin), oxytetracycline (Terramycin), and chlorotetracycline (Aureomycin) are closely related structurally and in their antibiotic activity. They are "broad-spectrum" antibiotics, effective against many Gram-positive and Gram-negative bacteria, rickettsiae, certain protozoa, and some viruses. The results have been especially good with Rocky Mountain spotted fever, typhus, pneumonia, scarlet fever, and gonorrhea.

## ► QUESTIONS

1. Show by equations how *o*-cresolphthalein could be prepared.
2. Show how *o*-cresolphthalein would behave on treatment with alkali.
3. The common type of quinone is exemplified by 1,4-benzoquinone. A second type of quinone can be obtained by the careful oxidation of catechol. Write its formula.



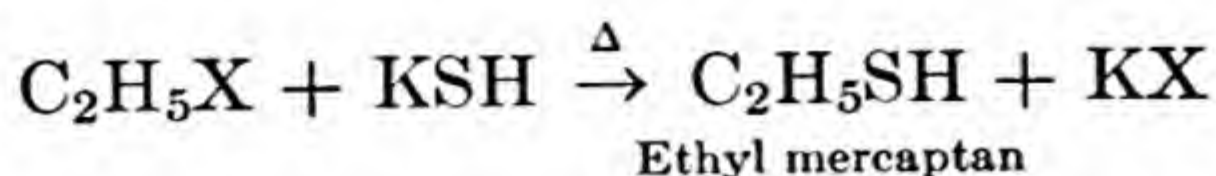
Because it can have three different valences sulfur forms numerous functional groups. The model shows dimethyl sulfone,  $\text{CH}_3\text{SO}_2\text{CH}_3$ , in which the sulfur may be considered hexavalent.

Sulfur is in the same group of the periodic table as oxygen, and it is therefore not surprising that there are sulfur-containing groups analogous to those containing oxygen. The properties of compounds containing such groups are similar in many ways to their oxygen counterparts. They differ in others because of the ability of the sulfur atom to exist in several oxidation states.

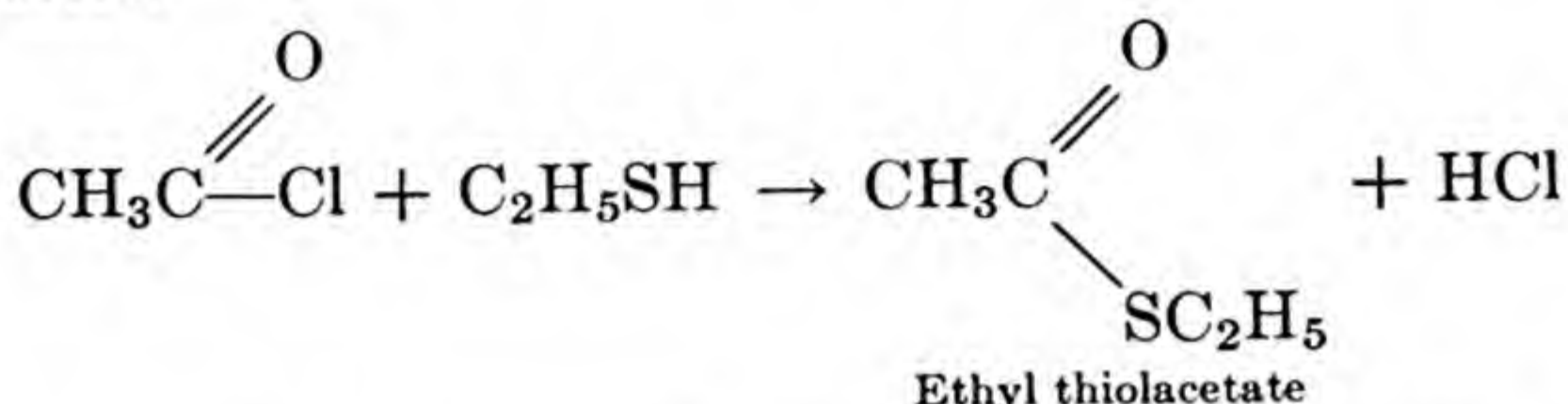
### ► MERCAPTANS

The mercaptans (thiols) are the sulfur analogs of the alcohols. They can be prepared by the reaction of sodium or potassium hydrogen sulfide with an alkyl halide.

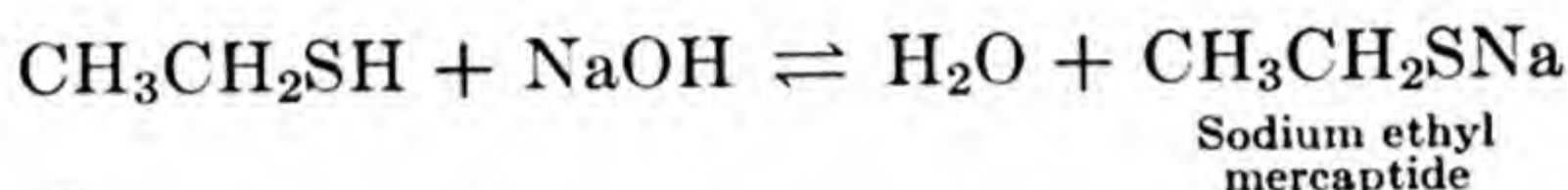




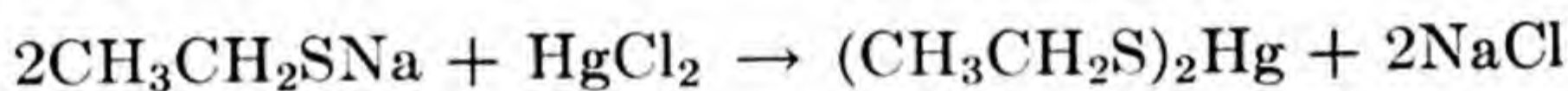
Some of the reactions of the mercaptans are like those of the alcohols. For example, they react with acid chlorides or anhydrides to yield esters.



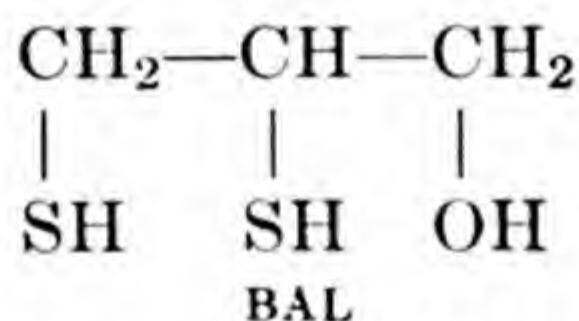
They are somewhat more acidic than the alcohols, and even with sodium hydroxide appreciable amounts of the sodium derivative are formed.



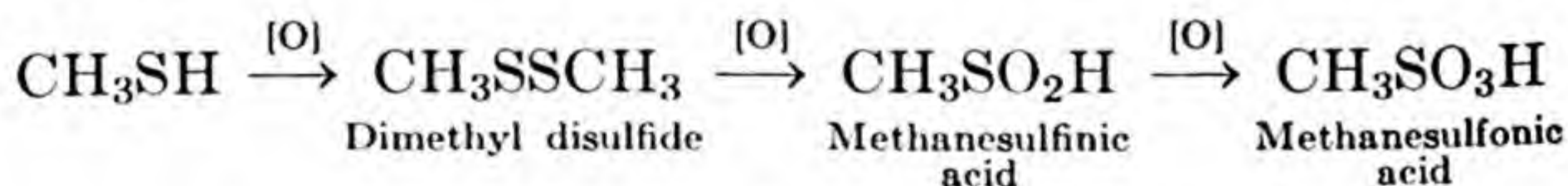
Heavy metal mercaptides are not water-soluble, so that if the salt of a heavy metal is added to a solution of the sodium mercaptide the derivative precipitates. Indeed, the name derives from the fact that



mercaptans can be made to react with mercury compounds. The principle of action of BAL (British Anti-Lewisite; 2,3-dimercapto-propanol) as an antidote in heavy metal poisoning is the same.



The contrast in the oxidation of the alcohols and mercaptans is an interesting one. With the former, the reaction proceeds in different ways, depending on whether the alcohol is primary, secondary, or tertiary (p. 60). The mercaptans, however, all undergo oxidation in the same way; several stages are involved, and a sulfonic acid is the final product.

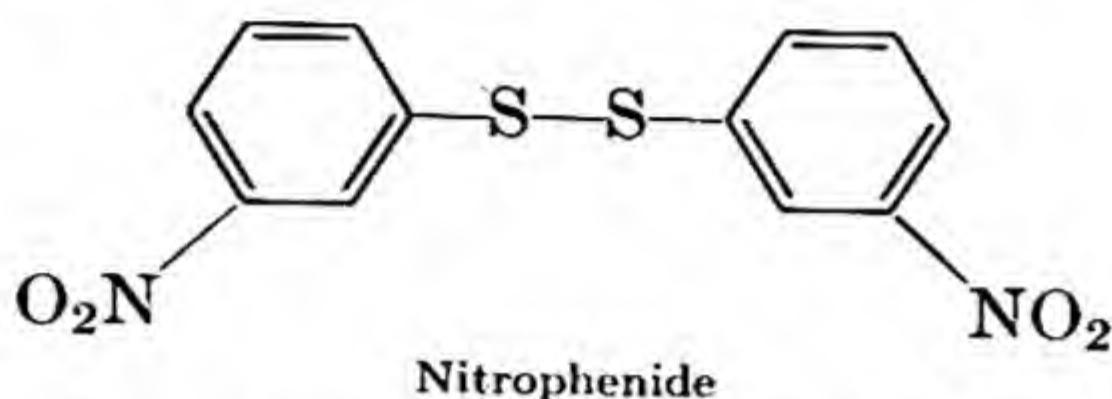


All mercaptans have disagreeable odors detectable in very high dilution. The odor of the skunk is due at least in part to the presence of *n*-butyl mercaptan, and a mixture of amyl mercaptans is used

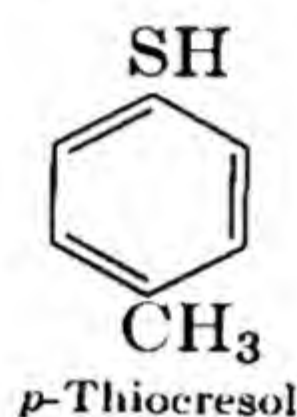
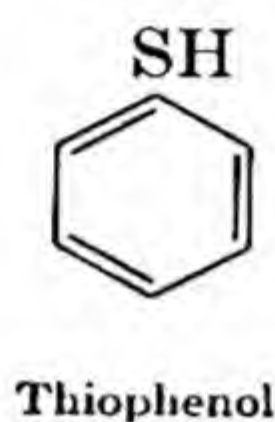


to impart an odor to natural or manufactured gases. The untreated gases have no odor, but the presence of the mercaptan enables the ready detection of leaks. Thioglycolic acid,  $\text{HSCH}_2\text{COOH}$ , is an ingredient of cold-wave preparations for the hair.

Nitrophenide, a disulfide, is incorporated into certain fowl feeds to prevent coccidiosis.

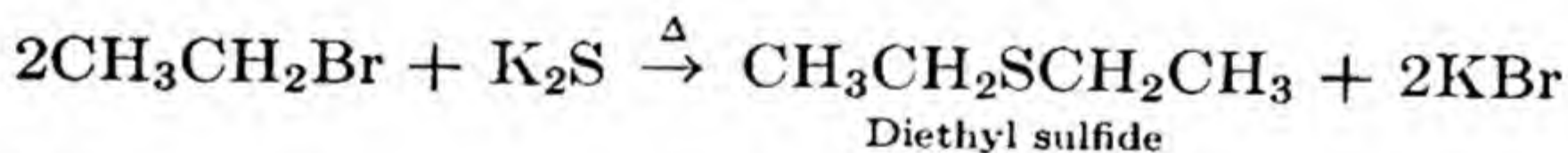


Sulfur analogs of the phenols are called thiophenols. Their chemical properties are like those of the mercaptans.



## ► SULFIDES

The sulfur analogs of the ethers are called thioethers or sulfides. The most general preparative method involves the reaction of a “neutral” alkali-metal sulfide with an alkyl halide.



Like their oxygen counterparts, the thioethers are rather unreactive. They are readily oxidized, however, and as in the mercaptans the sulfur is affected.



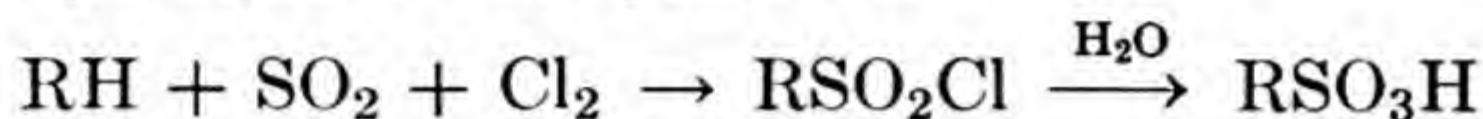
Sulfides have been used as chemical warfare agents. Mustard gas (actually an oily liquid) was an important weapon in World War I. It was prepared from ethylene and sulfur monochloride,  $\text{S}_2\text{Cl}_2$ . Sesquimustard was discovered during World War II but was not used. The most obvious physiological property of these substances is their vesicant, i.e., blister-producing effect.





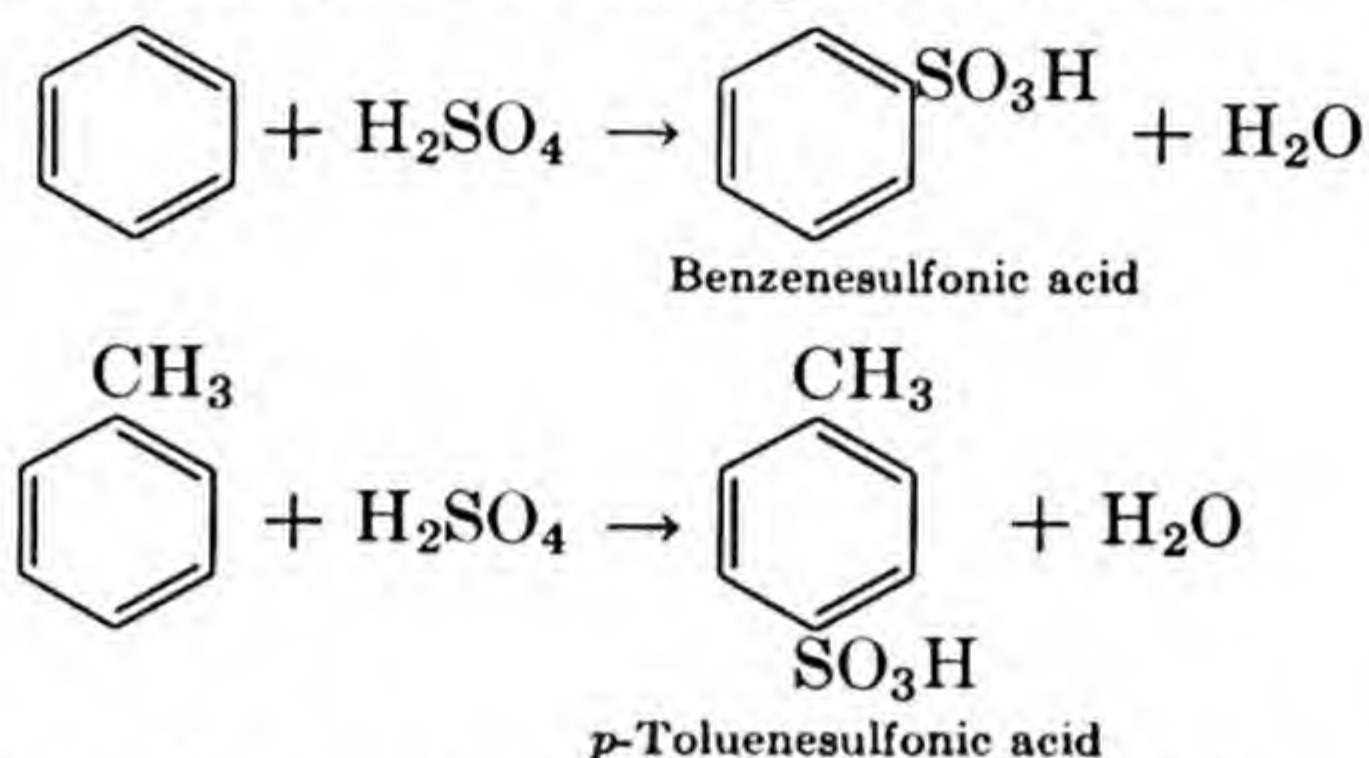
## ► SULFONIC ACIDS

It was previously shown that the oxidation of mercaptans yields sulfonic acids,  $\text{RSO}_3\text{H}$ . Aliphatic sulfonic acids can also be made by treatment of paraffins with a mixture of sulfur dioxide and chlorine followed by hydrolysis of the products.

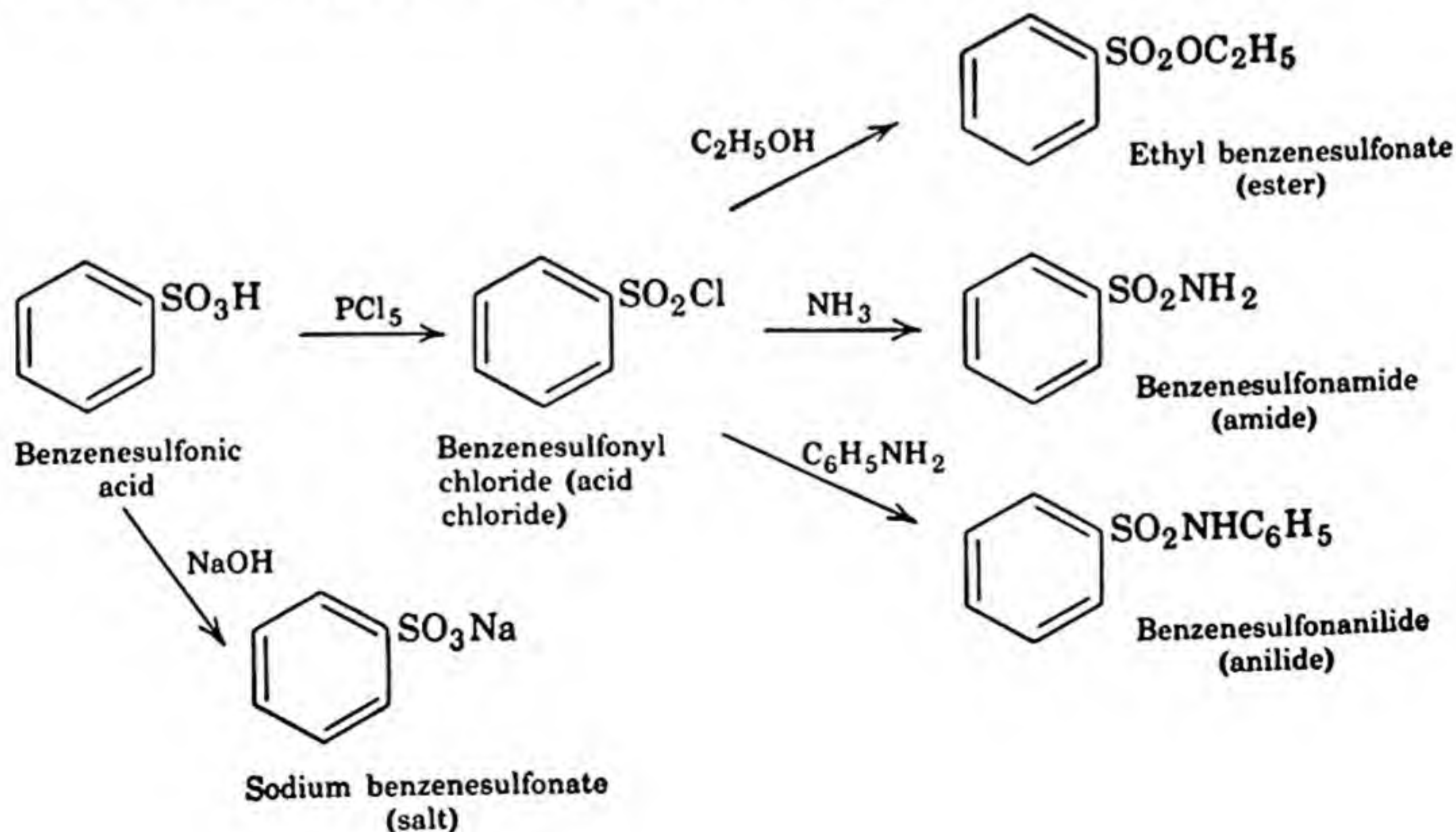


The first reaction, called chlorosulfonation, yields mixtures except in special cases.

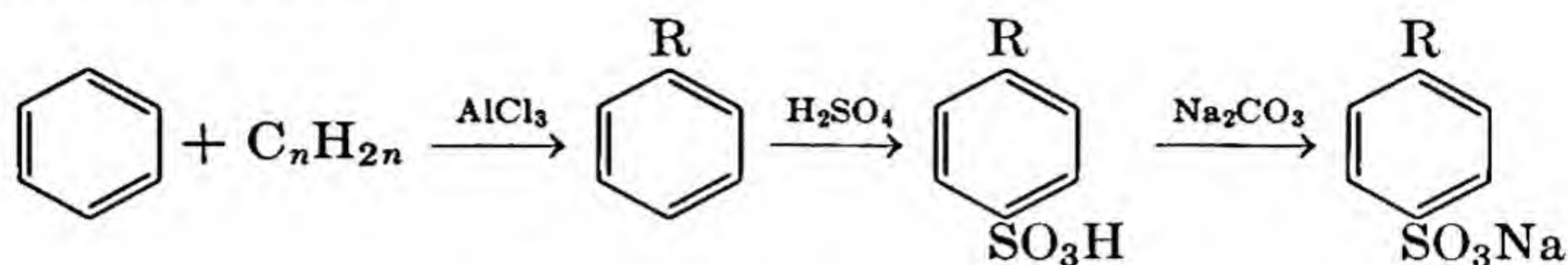
Aliphatic sulfonic acids are less important than their aromatic counterparts. The latter are nearly always prepared by direct sulfonation with concentrated or fuming sulfuric acid.



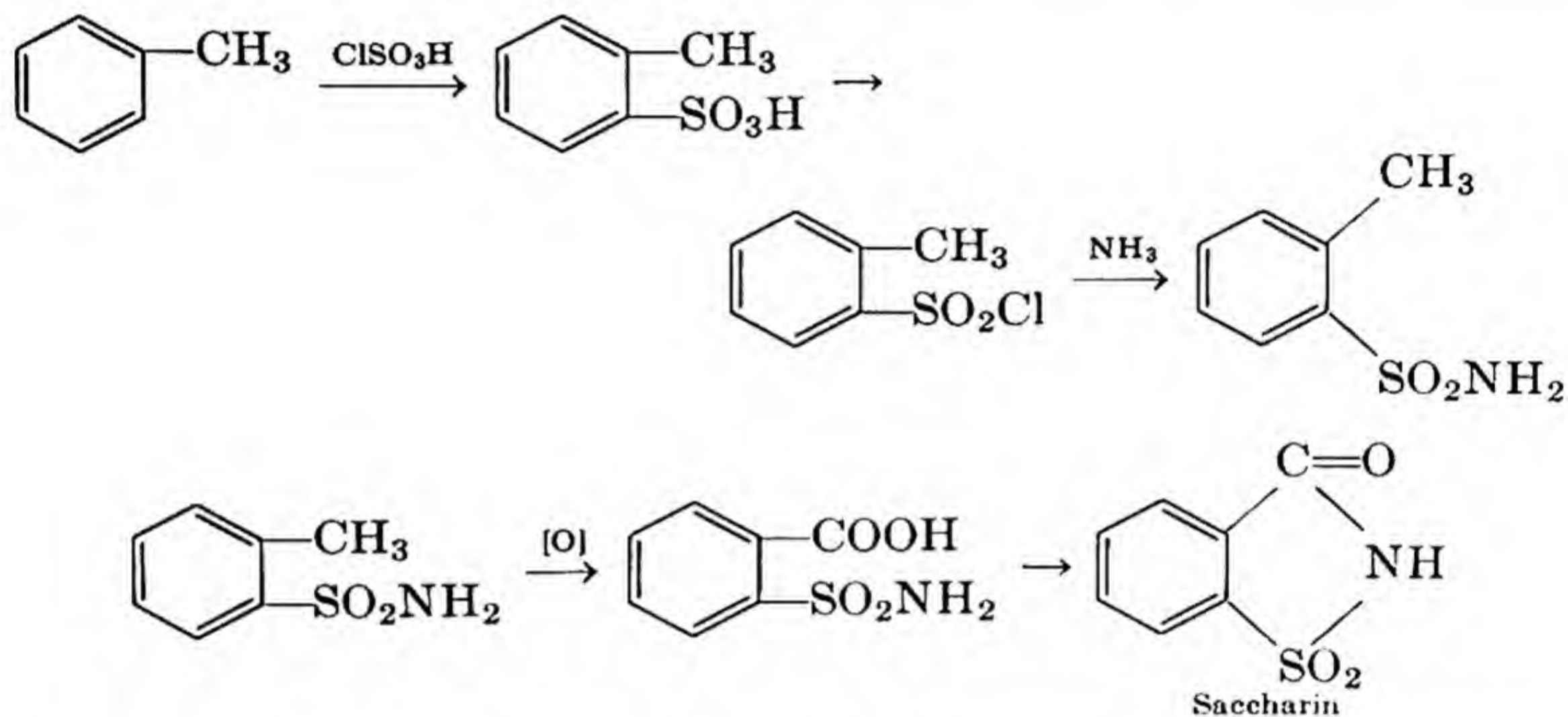
The sulfonic acids are strong acids, comparable to sulfuric acid. The sulfonic acid group promotes water-solubility; hence we often find that dyes, for example, contain one or more such groups. Many synthetic detergents are sodium salts of sulfonic acids. The sulfonic acids form a series of derivatives which correspond well to the derivatives of the carboxylic acids. The following chart shows some of these derivatives and their relationships to each other.



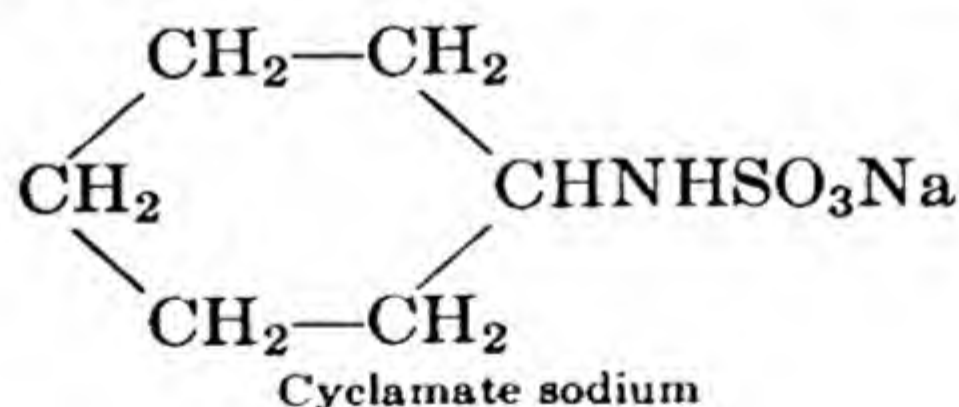
Many synthetic household detergents are aromatic sulfonates. In their preparation benzene is alkylated with a mixture of unsaturated hydrocarbons; the product, an alkylbenzene, is sulfonated, then converted into a salt.



Toluene is a source material for the manufacture of saccharin, a sweetening agent. Saccharin has no food value and indeed is excreted in the urine without chemical change.



Cyclamate (cyclohexanesulfamic acid) is also widely employed as a synthetic sweetening agent in the form of its sodium salt.



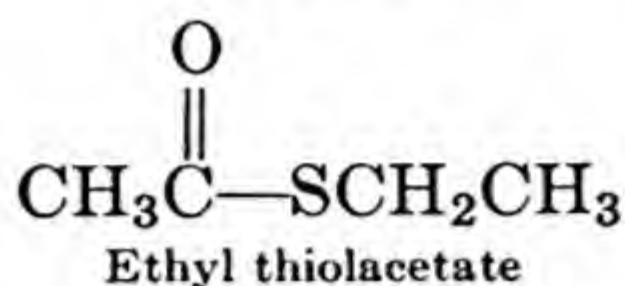
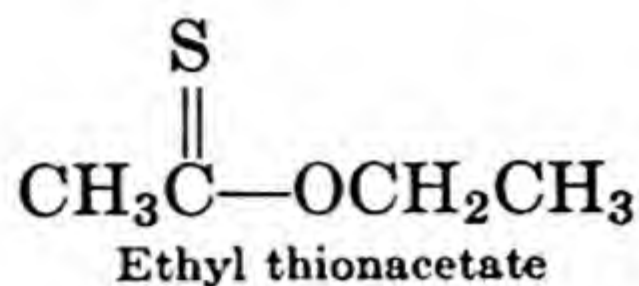
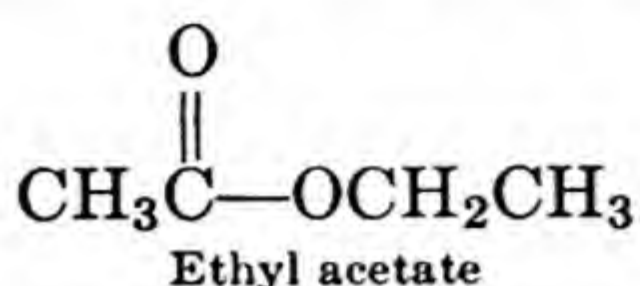
## ► OTHER SULFUR COMPOUNDS

Numerous other sulfur-containing functional groups are known. A few thioketones,  $\text{RCR}=\text{S}$ , have been described, but thioaldehydes are un-

stable. Three series of esters are known in which one or both of the



oxygen atoms are replaced by sulfur:

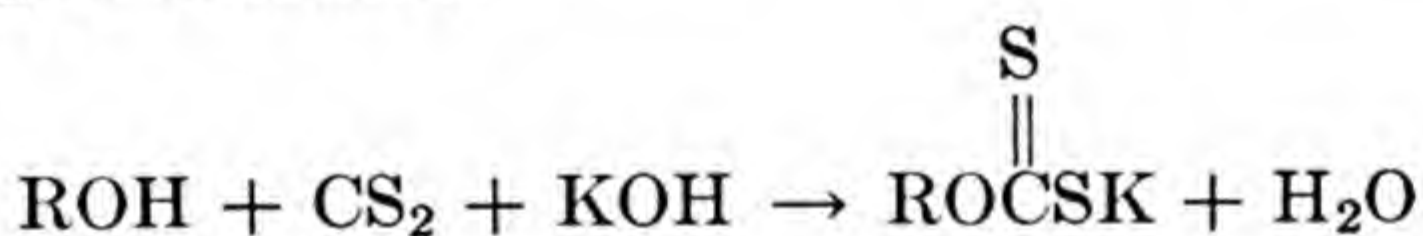


Alkyl thiocyanates are formed when alkyl iodides are treated with metal thiocyanates. They undergo rearrangement to isothiocyanates upon heating.

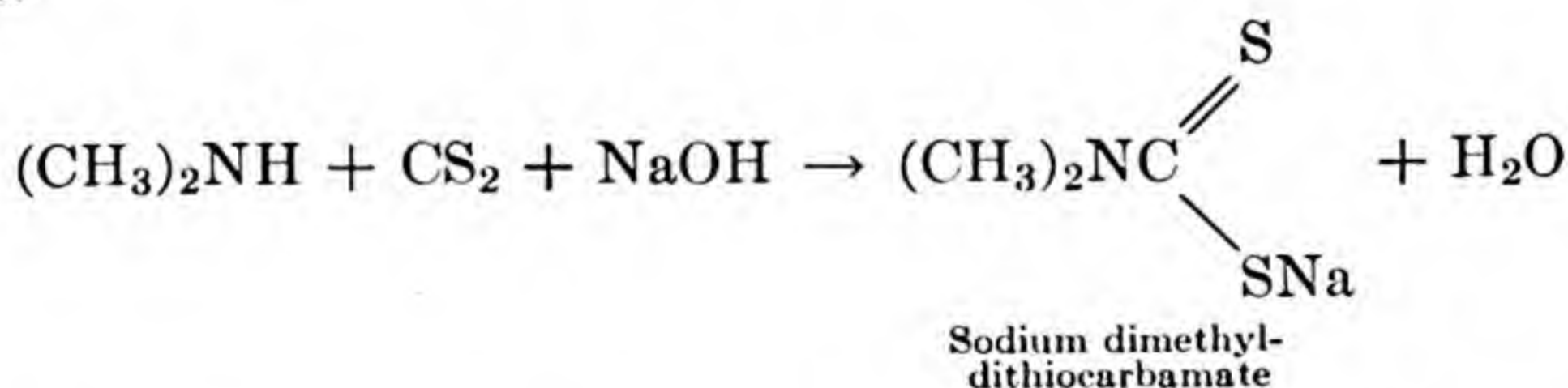


Isothiocyanates are sometimes called "mustard oils"; allyl isothiocyanate,  $\text{CH}_2=\text{CHCH}_2\text{NCS}$ , occurs in mustard and horse-radish.

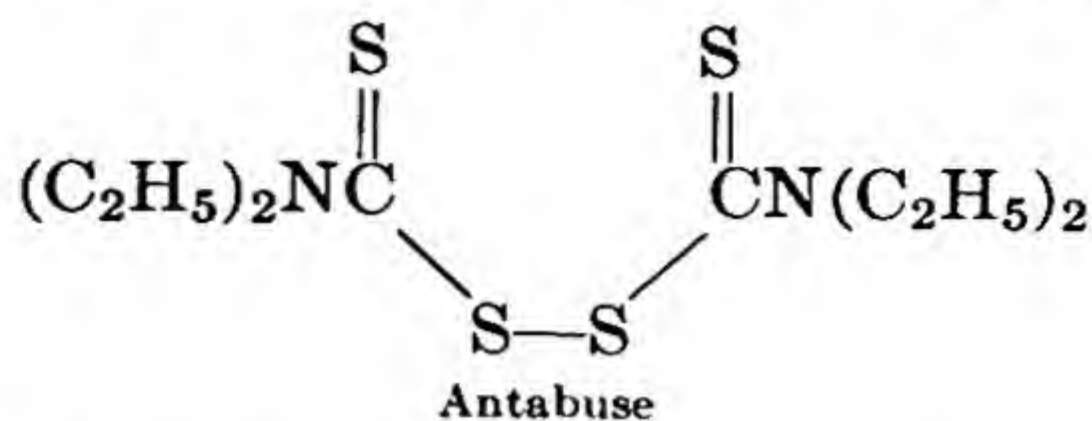
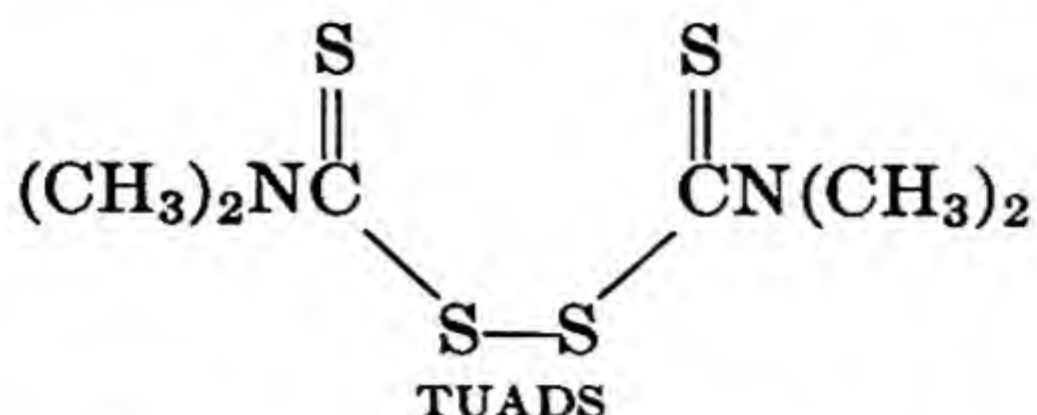
Carbon disulfide,  $\text{CS}_2$ , a dangerously inflammable liquid of low boiling point, is the starting material for the preparation of a number of sulfur compounds. Thus alcohols react with it in the presence of a base to give xanthates.



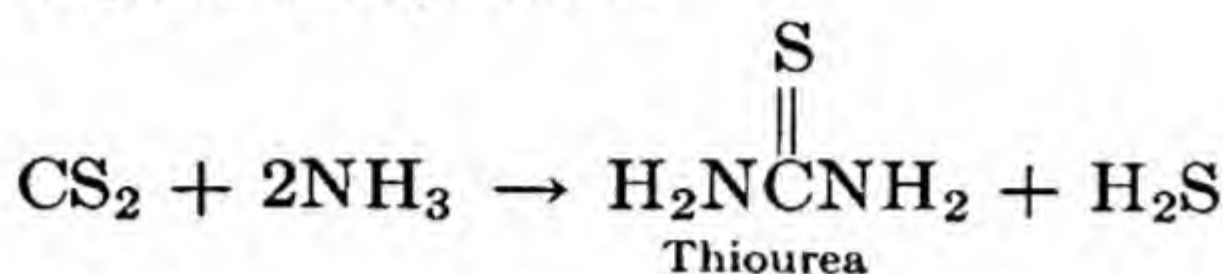
This reaction is the basis for the manufacture of viscose rayon (p. 173). Secondary amines react in a similar way to yield dithiocarbamates.



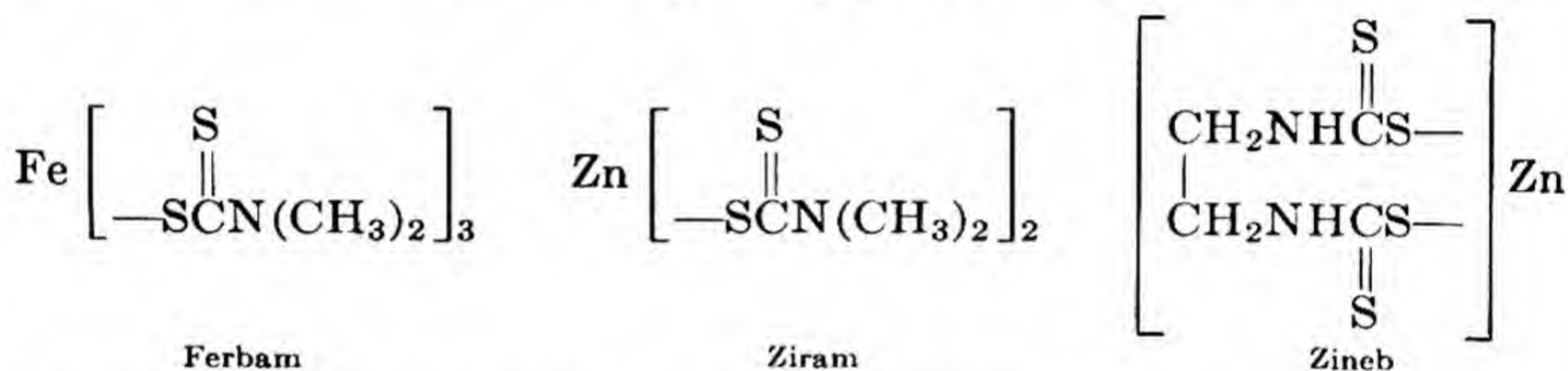
The oxidation of sodium dimethyldithiocarbamate with hydrogen peroxide furnishes tetramethylthiuram disulfide (TUADS), used as an accelerator in the vulcanization of rubber. The tetraethyl analog (Antabuse) has been used in the treatment of chronic alcoholism. It stops the normal oxidation of ethyl alcohol at the acetaldehyde stage. Accumulation of the aldehyde causes sickness which discourages further imbibing of alcohol.



Thiourea, the sulfur analog of urea, is prepared from carbon disulfide and ammonia. It has found application in silver cleaners and in the synthesis of heterocyclic compounds.

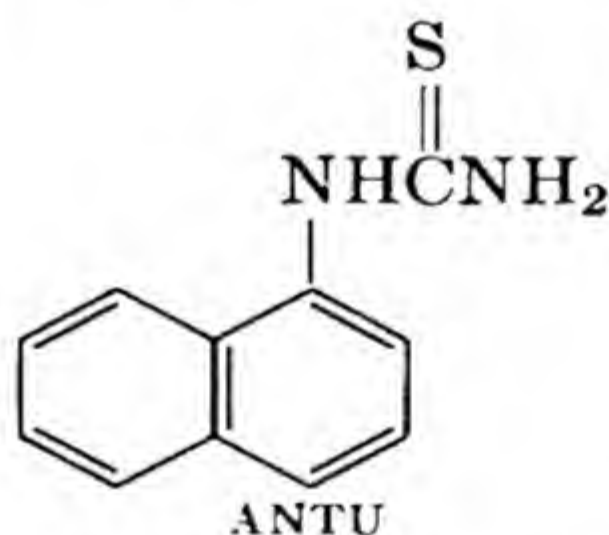


A number of valuable agricultural chemicals are sulfur-containing compounds. For example, certain metallic dithiocarbamates have been found effective as fungicides, particularly with truck crops.

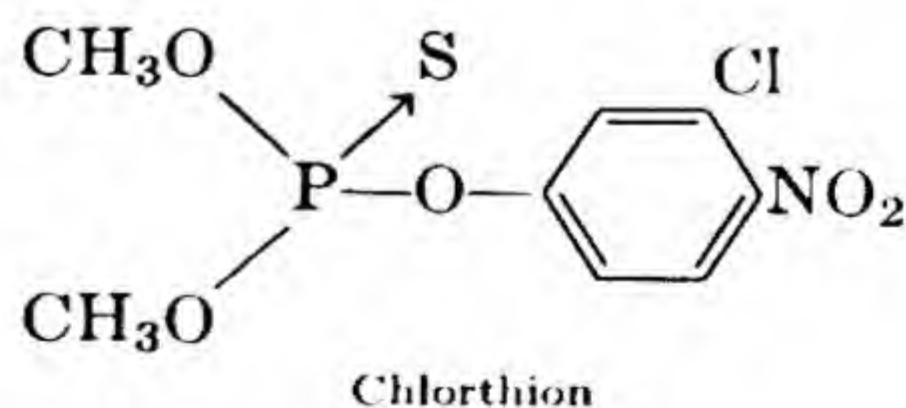
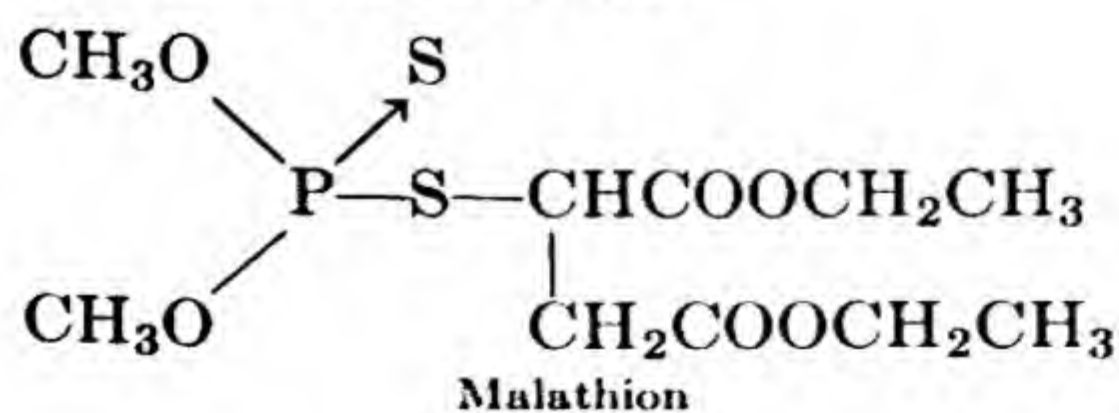


Iron, zinc, and manganese salts are employed for this purpose.

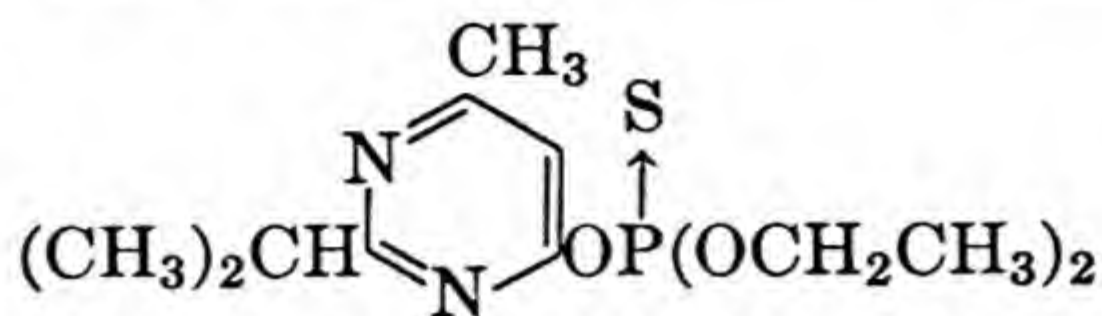
$\alpha$ -Naphthylthiourea (ANTU) has found application as a rodenticide:



Numerous insecticides are compounds containing sulfur and phosphorus. Malathion, Chlorthion, and Diazinon are examples of such compounds used in fly sprays. The emergence of strains of flies resistant to DDT and methoxychlor created a problem partially solved by these insecticides.

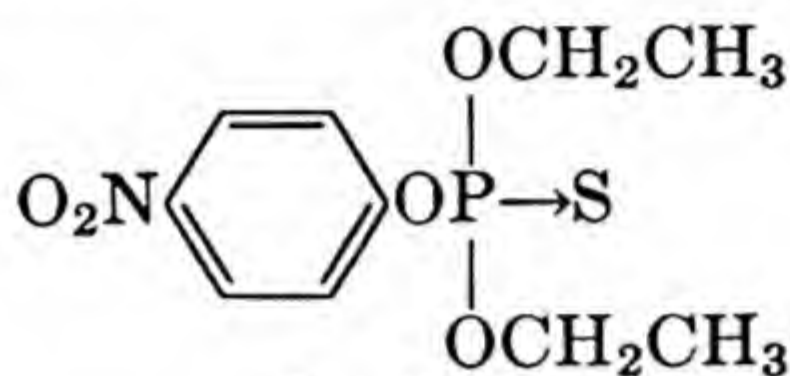




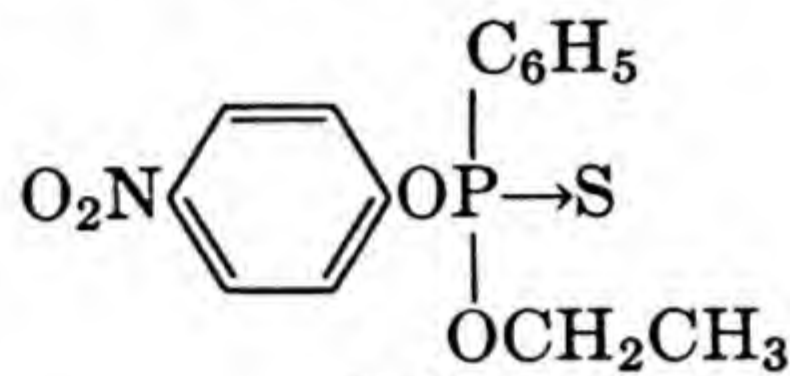


Diazinon

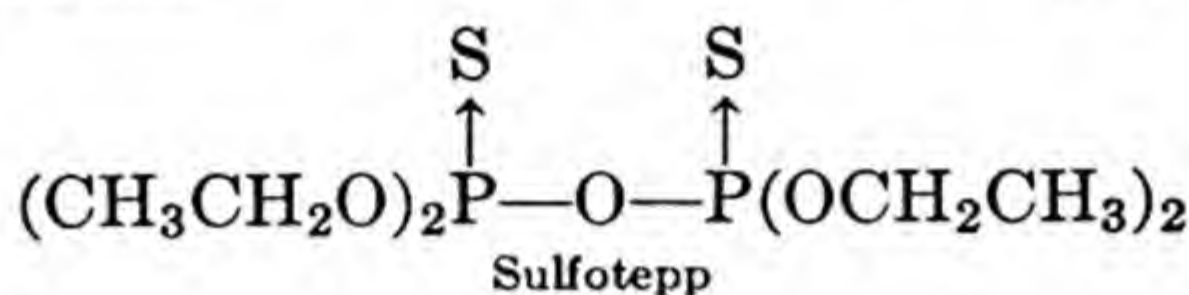
Certain other insecticides have found special usefulness in the protection of fruit trees. Some examples are given below:



Parathion



EPN



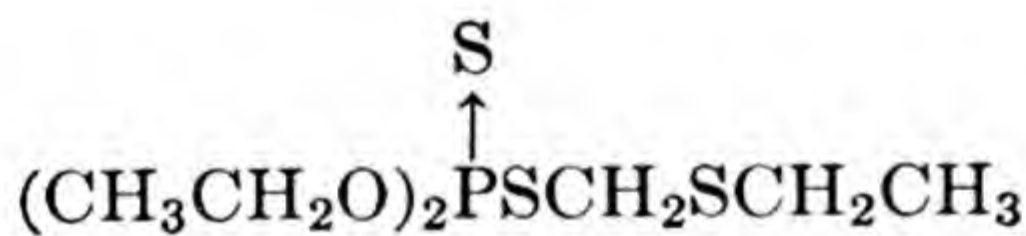
Sulfotepp



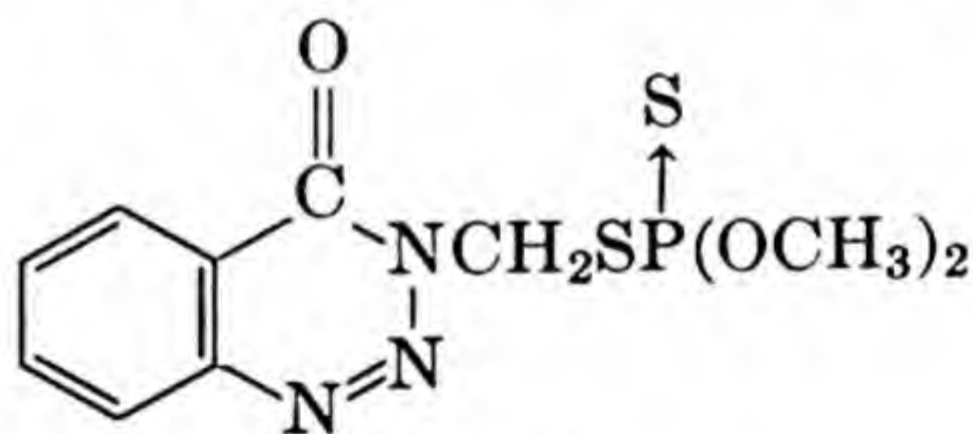
Systox; Demeton

Systox belongs to a class of insecticides especially interesting because of their mode of action. They are absorbed by, and translocated in, the plant without any apparent harm to it. When an insect eats any part of the plant it ingests the poison.

Thimet and Guthion are employed largely against cotton pests.



Thimet



Guthion

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► QUESTIONS

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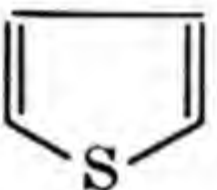
1. The decontamination of areas which have been in contact with mustard gas is of considerable military importance. With the knowledge that the sulfones are comparatively nontoxic, suggest a decontaminating agent for mustard gas.

2. Write structural formulas for sulfur analogs of the following oxygen-containing compounds and name them: acetic acid, acetone, carbon dioxide, ethyl ether.

3. Many medicinals are "elixirs," which are alcoholic solutions. Why would the use of Antabuse be undesirable for alcoholics who are also taking an elixir?



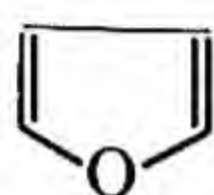


Thiophene, , shown in the model, has chemical and physical properties much like those of benzene. Because it occurs with the benzene obtained from coal tar its presence escaped detection for some time.

Compounds having rings with more than one kind of atom are said to be heterocyclic. Since the rings of organic compounds are primarily composed of carbon atoms, others in the ring are said to be hetero atoms. Those frequently found are oxygen, nitrogen, and sulfur, but many others are known to occur. Examples of heterocyclic compounds have been encountered in earlier chapters. The cyclic forms of the sugars have rings made up of carbon and oxygen as have the anhydrides of dibasic acids. Barbituric acid has a ring composed of carbon and nitrogen atoms. These compounds, though formally heterocyclic, are not usually classified as such by chemists because the ring structures contained in them are easily converted into open-chain compounds.

## ► AROMATIC HETEROCYCLIC COMPOUNDS

Many heterocyclic compounds have properties similar to those of benzene. The more important ones are depicted here. Compounds containing benzene rings condensed with heterocyclic rings are also well known. Many of them occur naturally or can be synthesized readily.



Furan



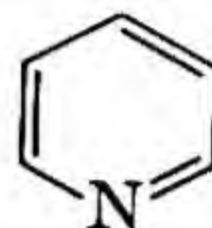
Pyrrole



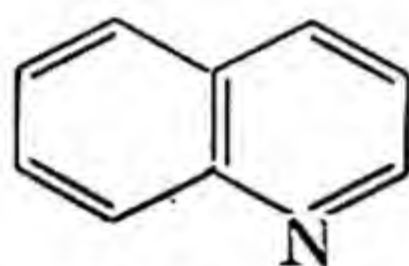
Thiophene



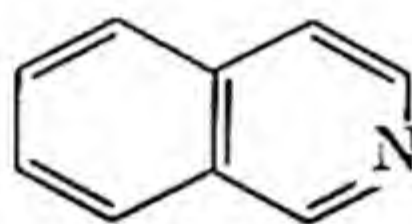
Thiazole



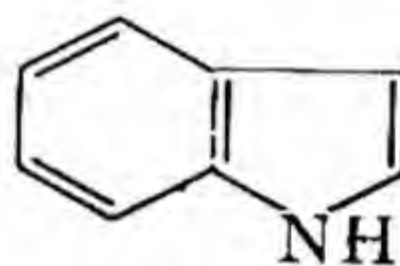
Pyridine



Quinoline



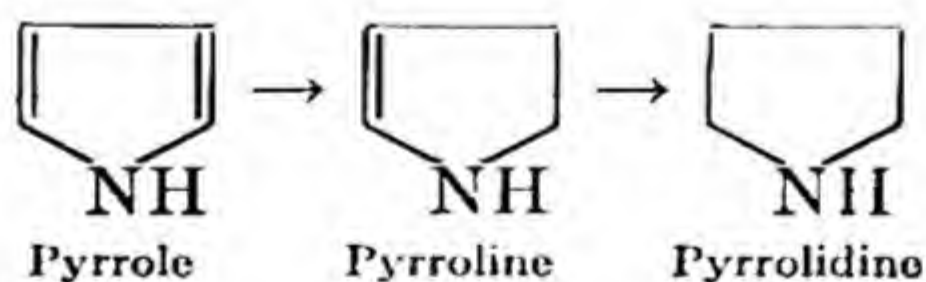
Isoquinoline



Indole

The chemistry of the aromatic heterocyclic compounds is in general more complex than that of benzene. Inspection of the formulas of furan, pyrrole, and thiophene shows that in each case there are two theoretically possible monosubstitution products, whereas with benzene only one is possible. Three monosubstituted thiazoles are possible and three monosubstituted pyridines. The comparison is even more striking with condensed-ring compounds; two monosubstituted naphthalenes are possible, but there are seven monosubstitution products of quinoline and seven of isoquinoline.

Many heterocyclic rings, like benzene, can be reduced with hydrogen and a catalyst or by other means to yield products which are no longer aromatic.



Pyrrole

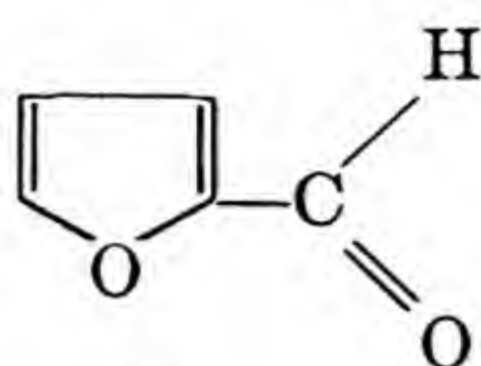
Pyrroline

Pyrrolidine

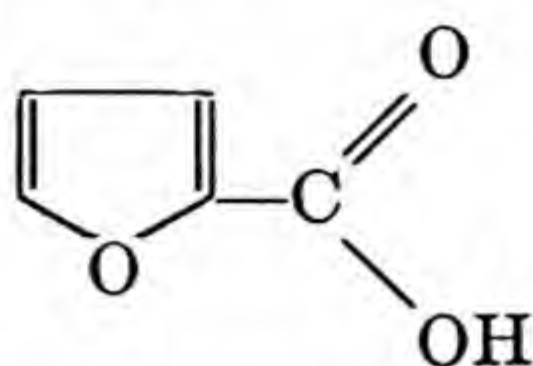
The number of known heterocyclic compounds is great, and space is not available to accord their chemistry the treatment it merits. Brief consideration only is therefore given to a few heterocyclic systems.

**Furan.** Furfural is obtained by the treatment of oat hulls, corn cobs, or cottonseed hulls with an acid. A pentosan present in these

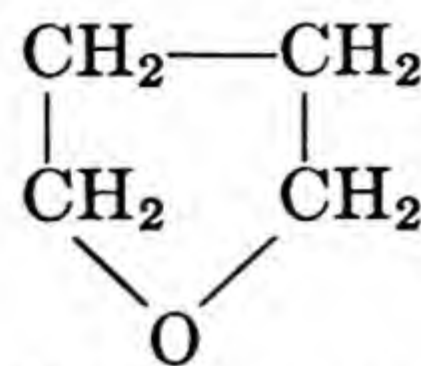




Furfural

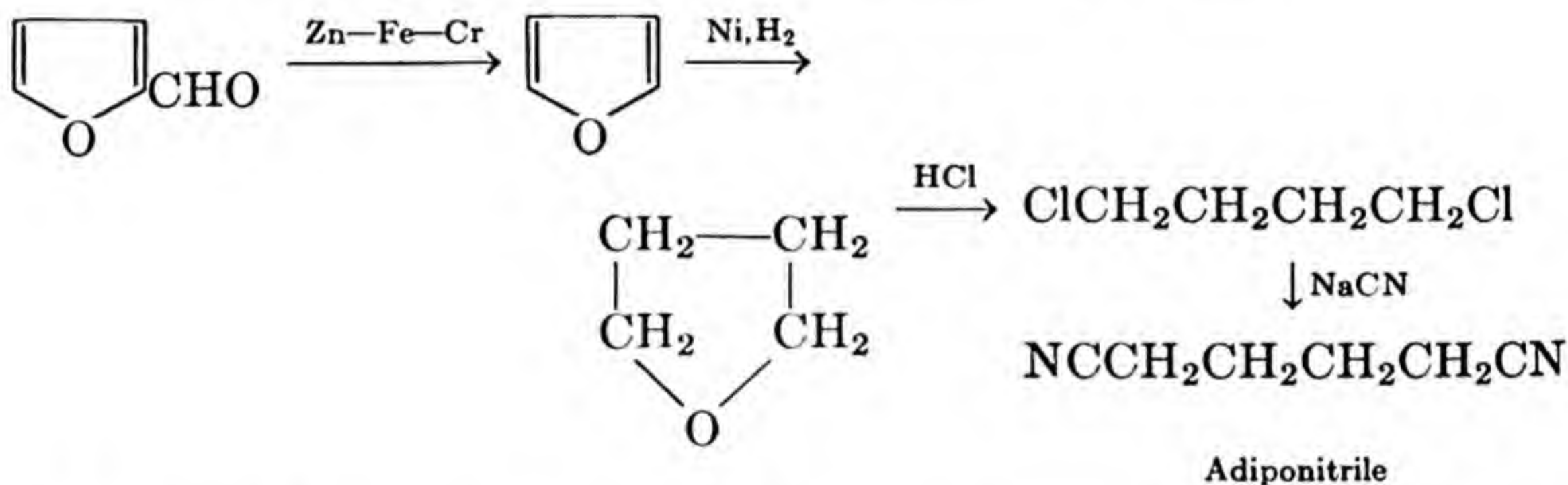


Furoic acid

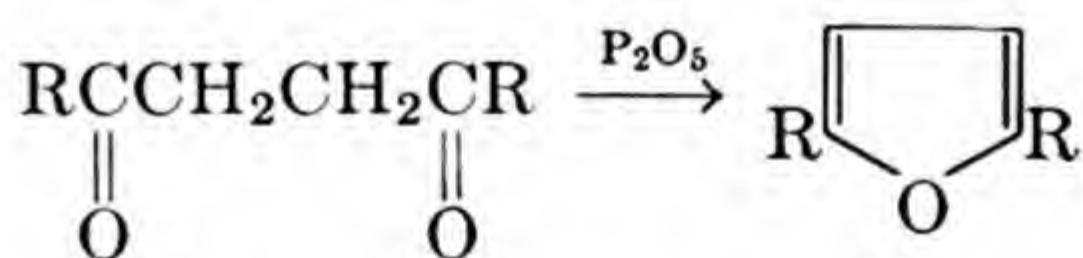


Tetrahydrofuran

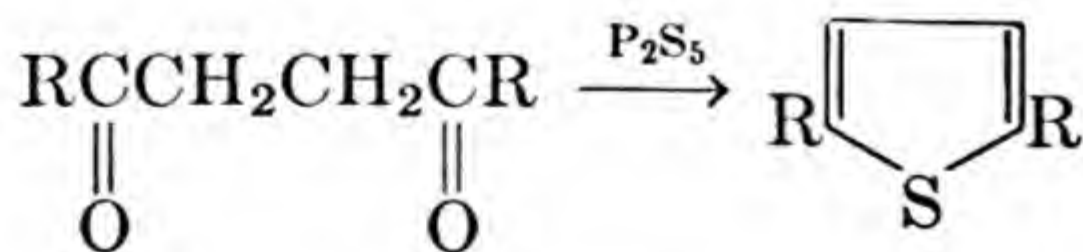
substances is the actual raw material. Furfural is a typical aromatic aldehyde which undergoes nearly all the reactions of benzaldehyde. It is readily convertible into other furan derivatives of value. Oxidation converts it to furoic acid, and in contact with certain metallic catalysts it is transformed into furan. This reaction is the basis for one of the processes used to prepare nylon intermediates. Adiponitrile, the final product of the series of reactions shown, can be hydrolyzed to adipic acid or hydrogenated to hexamethylenediamine, the two compounds needed to manufacture ordinary nylon.



A general method for making furans consists in the dehydration of 1,4-diketones.

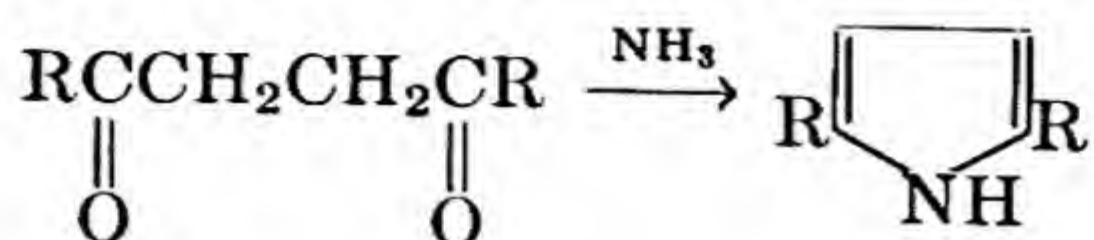


**Thiophene.** Thiophene occurs in coal tar and is obtained with benzene, which chemically it resembles very closely. This similarity delayed its discovery. Substituted thiophenes can be prepared by a general method similar to that for furans.



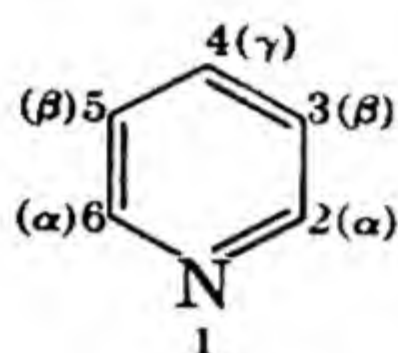
**Pyrrole.** Numerous derivatives of pyrrole occur naturally. The chlorophylls and hemoglobin are examples. Simple pyrroles can be made from 1,4-diketones and ammonia.



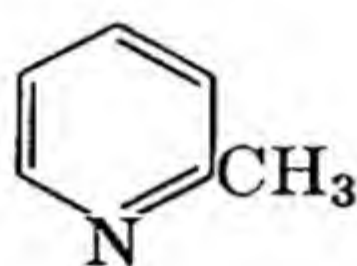


They are very weak acids; the hydrogen attached to the nitrogen is replaceable by metals.

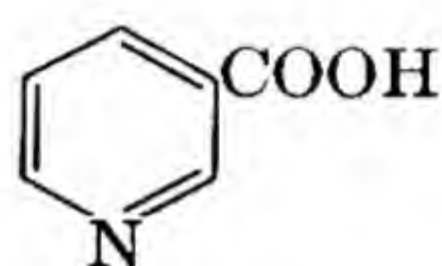
**Pyridine.** Coal tar contains pyridine and a number of substituted pyridines, particularly the methyl derivatives (picolines). They are liquids with a characteristic, disagreeable odor. Somewhat surprisingly, the simpler pyridine derivatives are very soluble in water. Pyridine derivatives in general are basic.



Pyridine

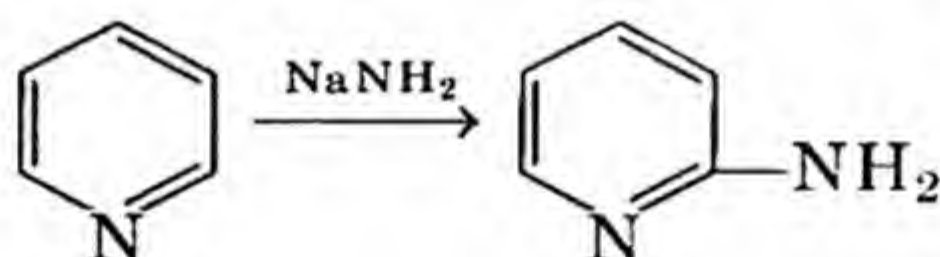


α-Picoline



Nicotinic acid

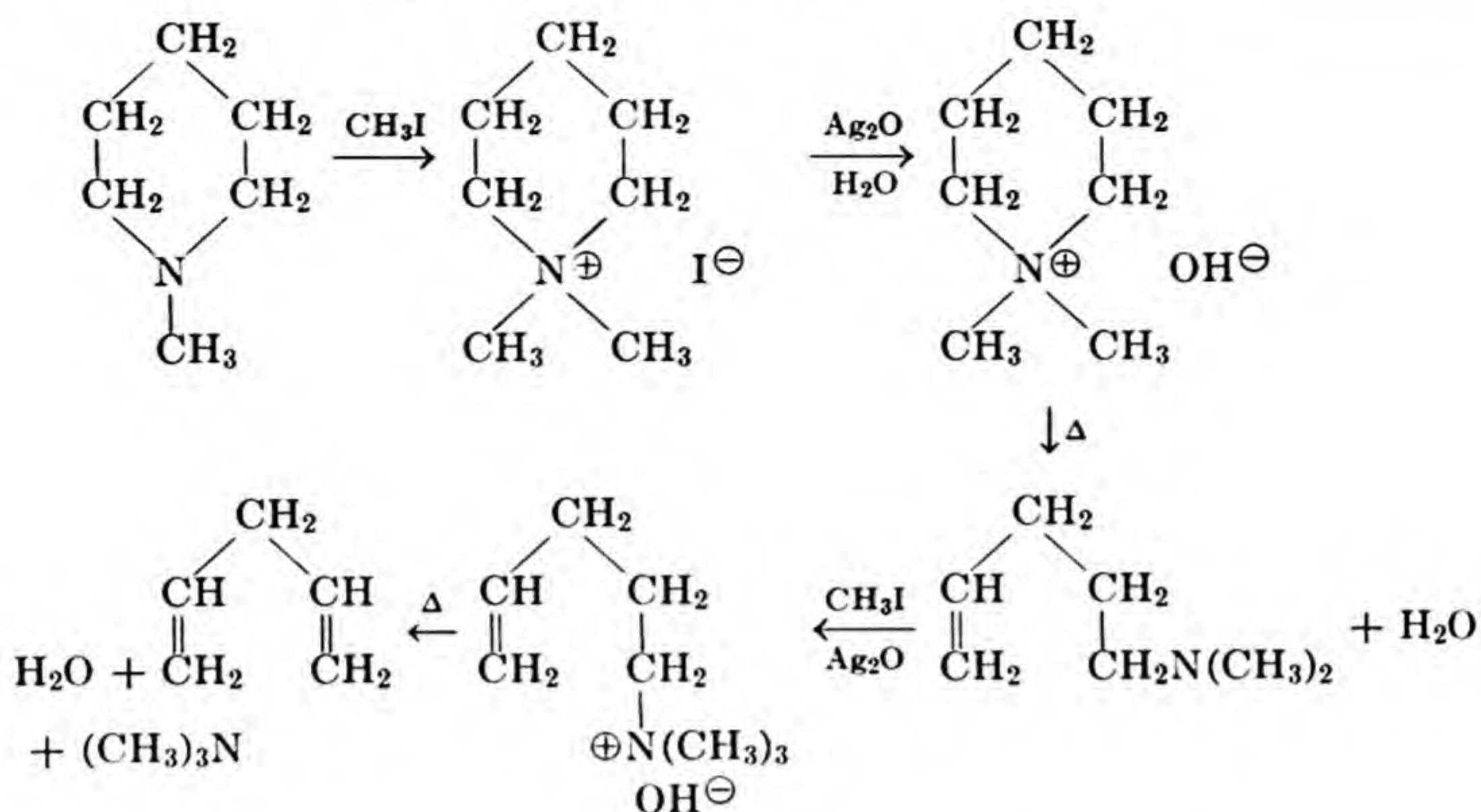
Pyridine undergoes substitution only with great difficulty when the usual reagents are used. The products are 3-substituted derivatives. Sodamide ( $\text{NaNH}_2$ ), however, readily yields 2-aminopyridine.



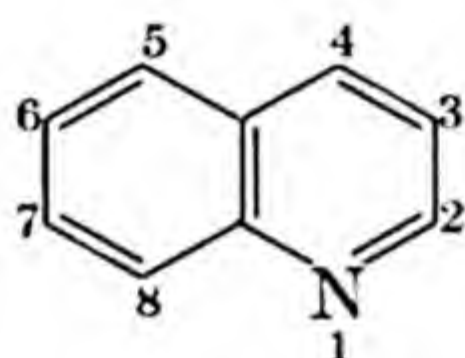
The reduction of pyridine, which is best done electrolytically, yields piperidine, the completely reduced substance. It is often used as a catalytic agent in condensation reactions. Piperidine derivatives occur naturally.

When *N*-methylpiperidine is treated with methyl iodide a quaternary ammonium iodide is formed, which upon treatment with a suspension of silver oxide in water yields the corresponding hydroxide. Heat converts the hydroxide, with loss of water, into an unsaturated straight-chain tertiary amine. The process may be repeated, and the final product is then a diene. The over-all series of reactions can be performed with many tertiary amines. It is called the Hofmann exhaustive methylation process and has proved to be helpful in determining the structures of natural products. Combined with other information, it may reveal the location of the nitrogen atoms and the size of rings present.

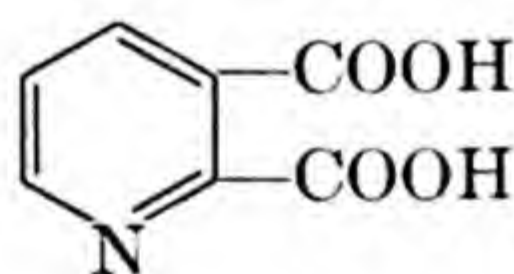




**Quinoline.** Quinoline and a number of its simple substitution products occur in coal tar. More complex derivatives are found in plants. The bark of the cinchona tree, for example, contains a number of quinoline alkaloids, including quinine.



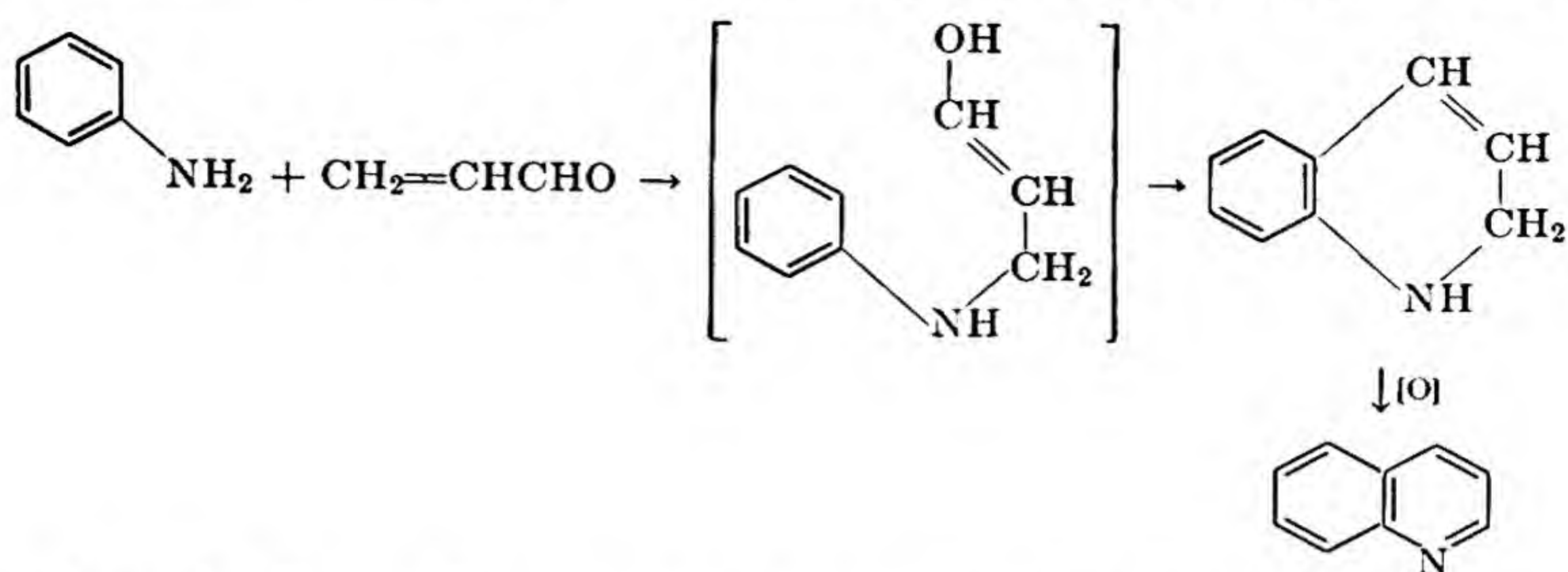
Quinoline



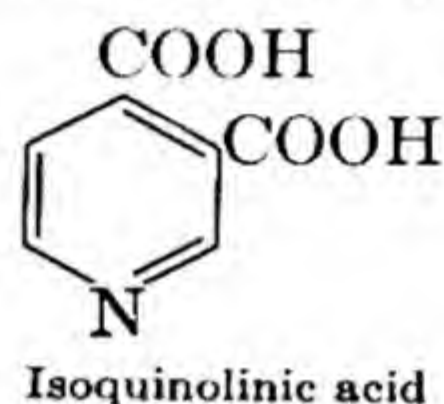
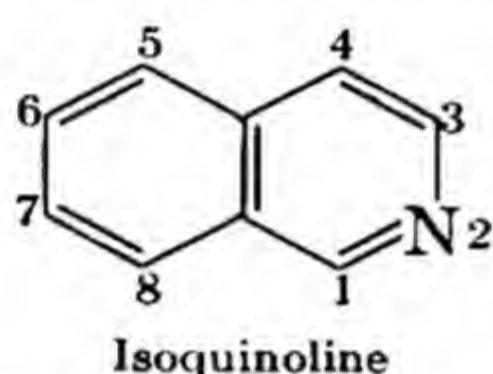
Quinolinic acid

The stability of the pyridine ring toward oxidation is demonstrated by the fact that vigorous oxidation of quinoline yields quinolinic acid, an intermediate in a commercial preparation of nicotinic acid, a vitamin. Because it forms colored complexes with a number of metallic ions 8-hydroxyquinoline is widely used in analytical chemistry.

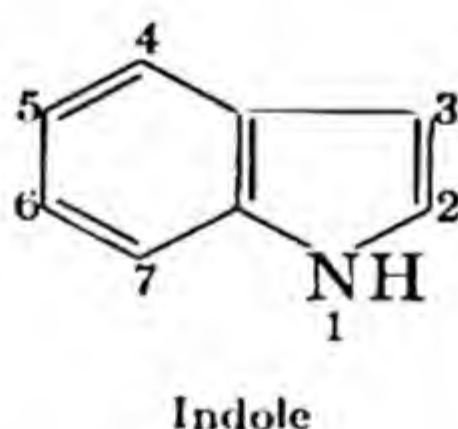
The Skraup reaction and modifications of it furnish a valuable route to various quinoline derivatives. Fundamentally, the synthesis of quinoline involves the reaction of aniline with acrolein in the presence of a mild oxidizing agent. In practice, glycerol is used in place of acrolein, and a dehydrating agent such as sulfuric acid is employed. Various moderators are also used to control the vigor of the reaction, which can otherwise get out of hand. Suitable modification of the aromatic amine or of the acrolein leads to various substituted quinolines.



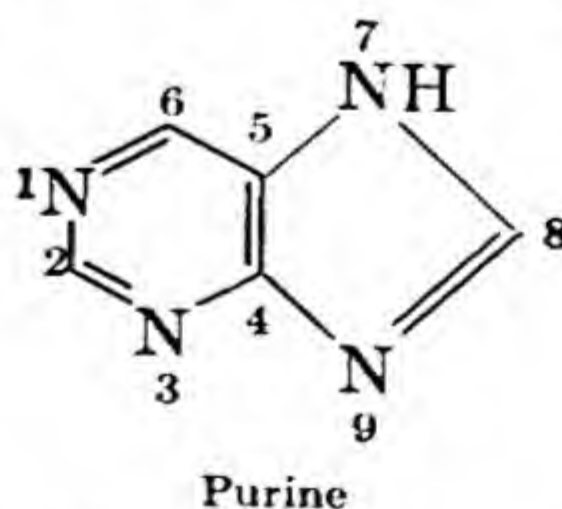
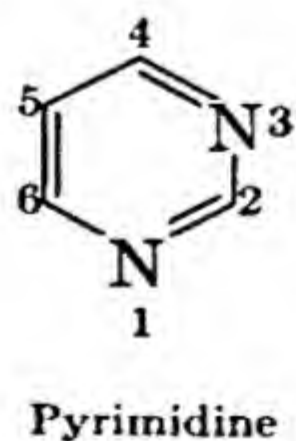
**Isoquinoline.** Compounds which contain the isoquinoline ring system occur naturally. Isoquinoline itself does not occur in very large amounts in coal tar, and it and its derivatives have to be synthesized. Vigorous oxidation of isoquinoline yields isoquinolinic acid.



**Indole.** Indole derivatives occur widely in nature. Tryptophan, one of the natural amino acids (Chapter 15), contains the indole system. Putrefying organisms in the large intestine convert tryptophan into indole and skatole (3-methylindole) which are eliminated in the feces.



**Purines and Pyrimidines.** A group of substances of special biological interest are the purines and pyrimidines. They are produced with other substances in the hydrolysis of nucleic acids. Yeast

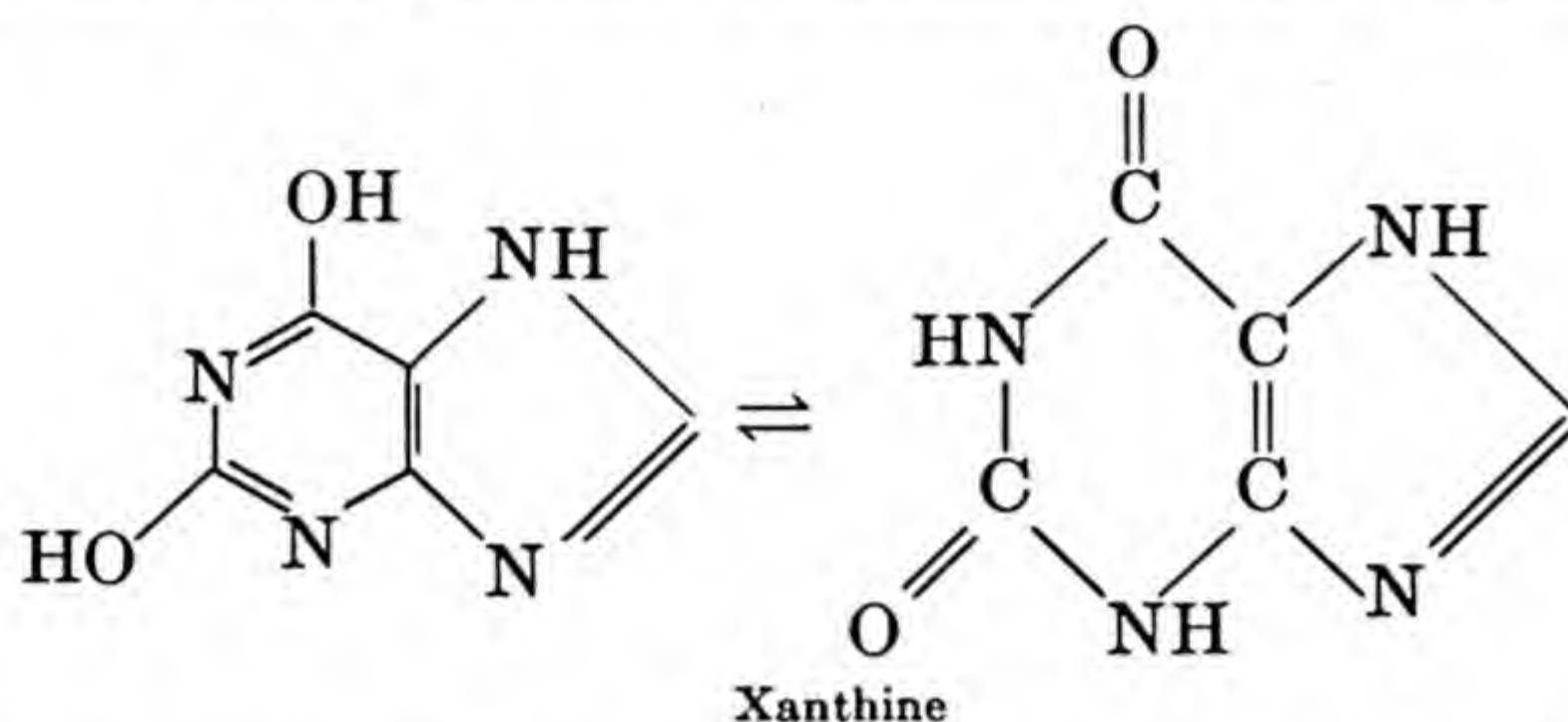


nucleic acid, for example, upon hydrolysis yields adenine (6-amino-purine), guanine (2-amino-6-hydroxypurine), cytosine (2-hydroxy-

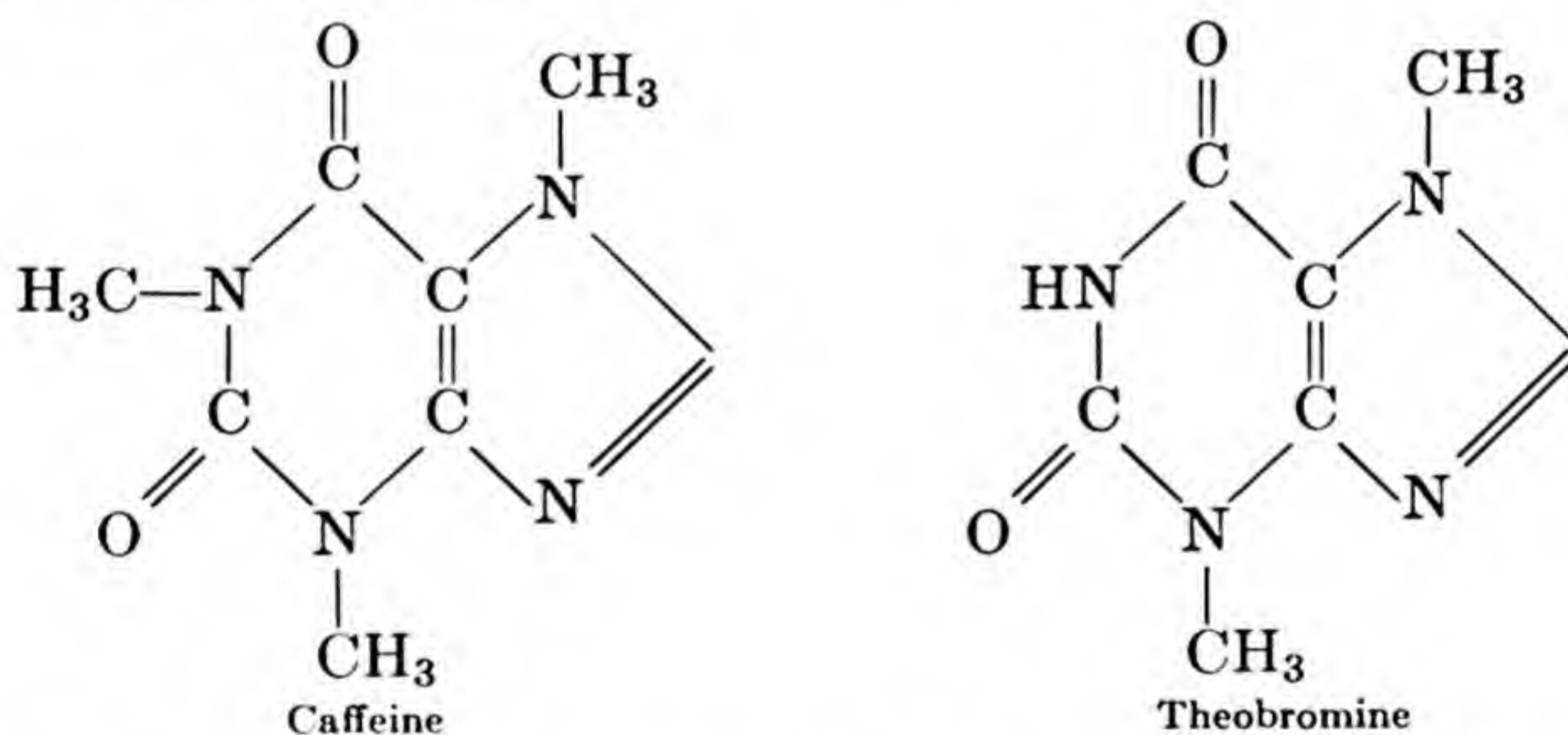


4-aminopyrimidine), and uracil (2,4-dihydroxypyrimidine). Thymus nucleic acid (from the thymus glands of hogs) yields the same compounds, except that thymine (2,4-dihydroxy-5-methylpyrimidine) results instead of uracil.

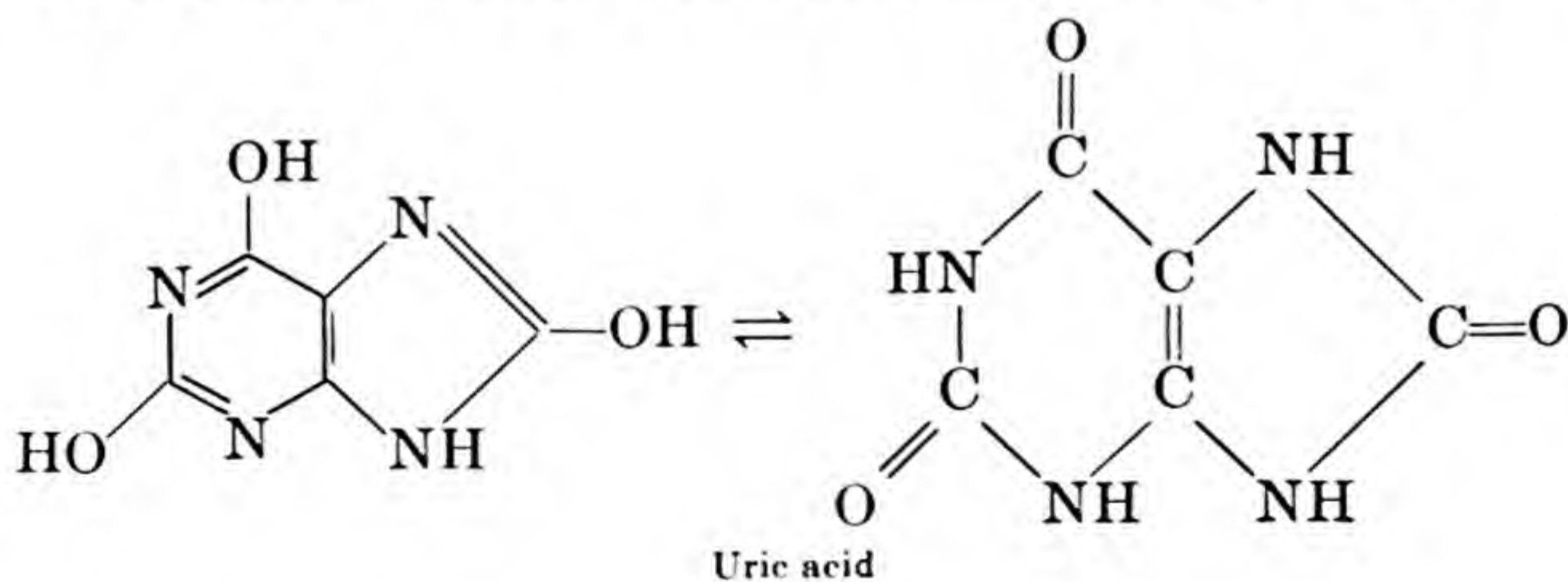
Purine derivatives occur in tea and coffee. The most important are caffeine and theobromine. Both are methylated derivatives of xanthine (2,6-dihydroxypurine). Xanthine, as well as other hydroxy-



and aminopurines, exists in tautomeric forms, which make it possible to have substituents on the nitrogen atoms. Caffeine and theobromine are both diuretics. Caffeine is a stimulant and is therefore used widely with antihistamines to counteract their sedative effect and in other similar applications.



Uric acid (2,6,8-trihydroxypurine) occurs in human urine as an end product of purine metabolism, and the amount excreted is variable. With some animals, however, it is the chief product of nitrogen

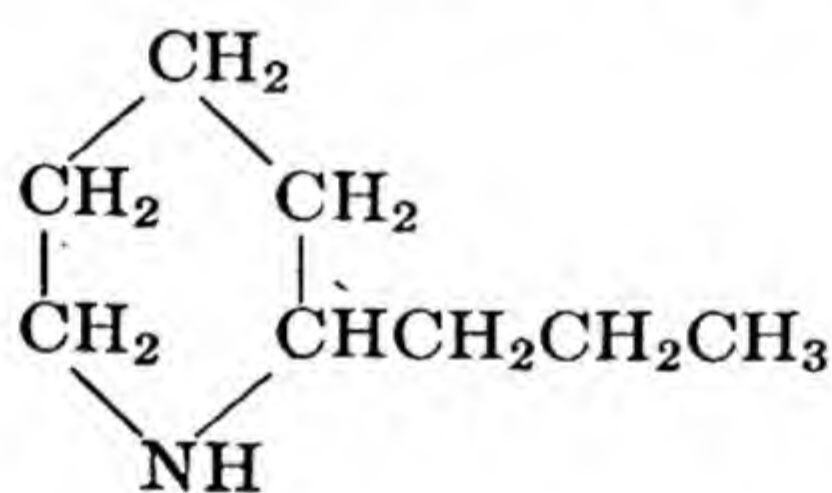


metabolism. Uric acid and its salts are not very soluble in water; urine containing appreciable amounts of urates will on standing gradually become cloudy. In gout sodium urate deposits in the tissues.

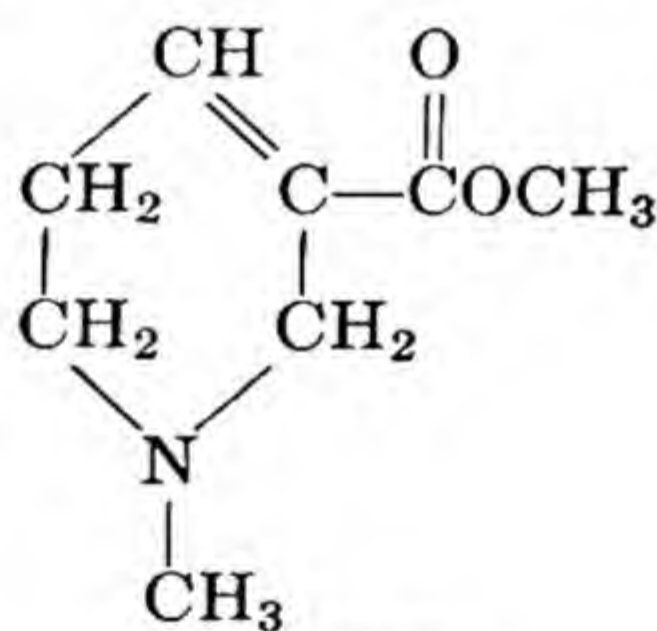
## ► ALKALOIDS

The alkaloids are a group of basic substances occurring in plants. They are varied in structure, but nearly all have at least one heterocyclic ring, and nearly all have some distinct physiological action. The alkaloids from a given plant are usually very similar in structure and are often classified by reference to the ring systems which they contain. To a certain extent this is also a biological classification because alkaloids of a type are often limited to a particular genus. Only a few of the more interesting alkaloids can be described here.

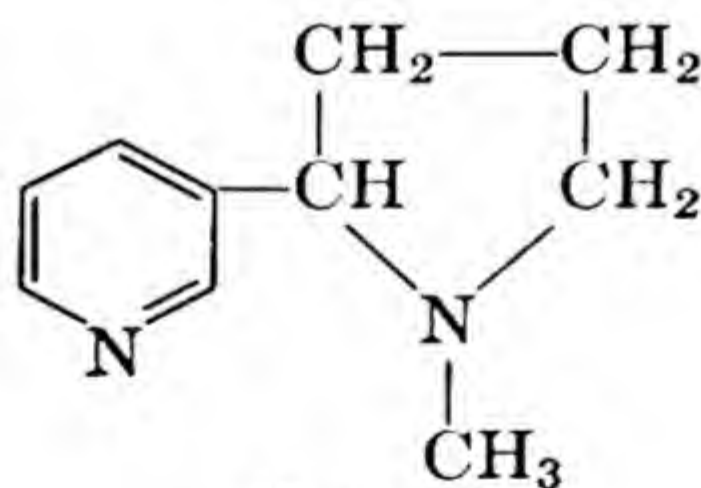
A number of the simpler alkaloids contain the pyridine ring, in some cases partially or completely reduced. Coniine, for example, occurs in the hemlock and is of historical interest as the substance responsible for the death of Socrates and as the first alkaloid to be synthesized. Arecoline is the active principle of the betel nut,



Coniine



Arecoline

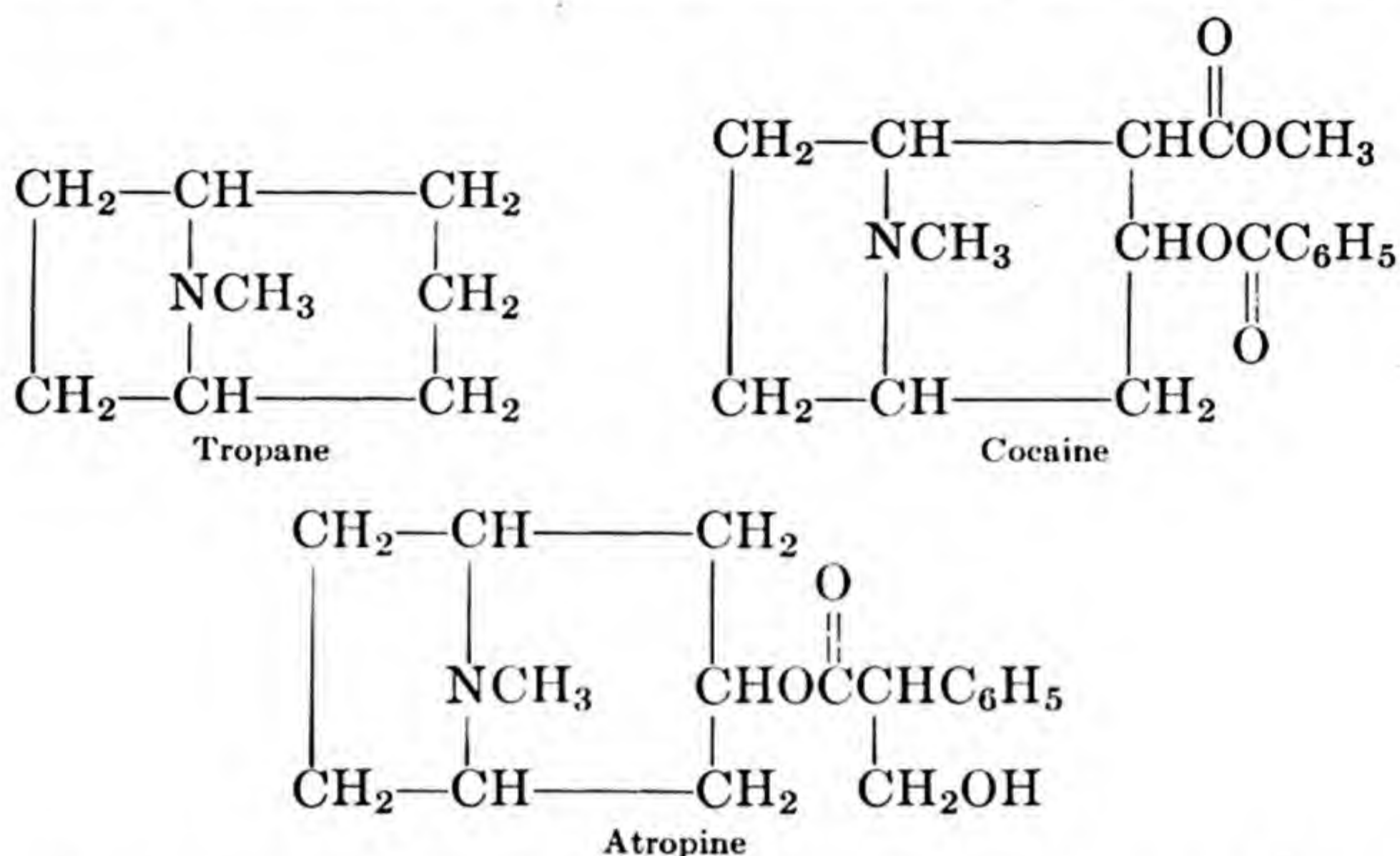


Nicotine

chewed habitually by several million Asians and Polynesians because it promotes a feeling of good humor and well-being. Nicotine is one of a number of structurally related alkaloids found in tobacco. Its extreme toxicity to animals is well known; forty milligrams has caused death to a human. Nicotine is an efficient insecticide but must be employed with great care.

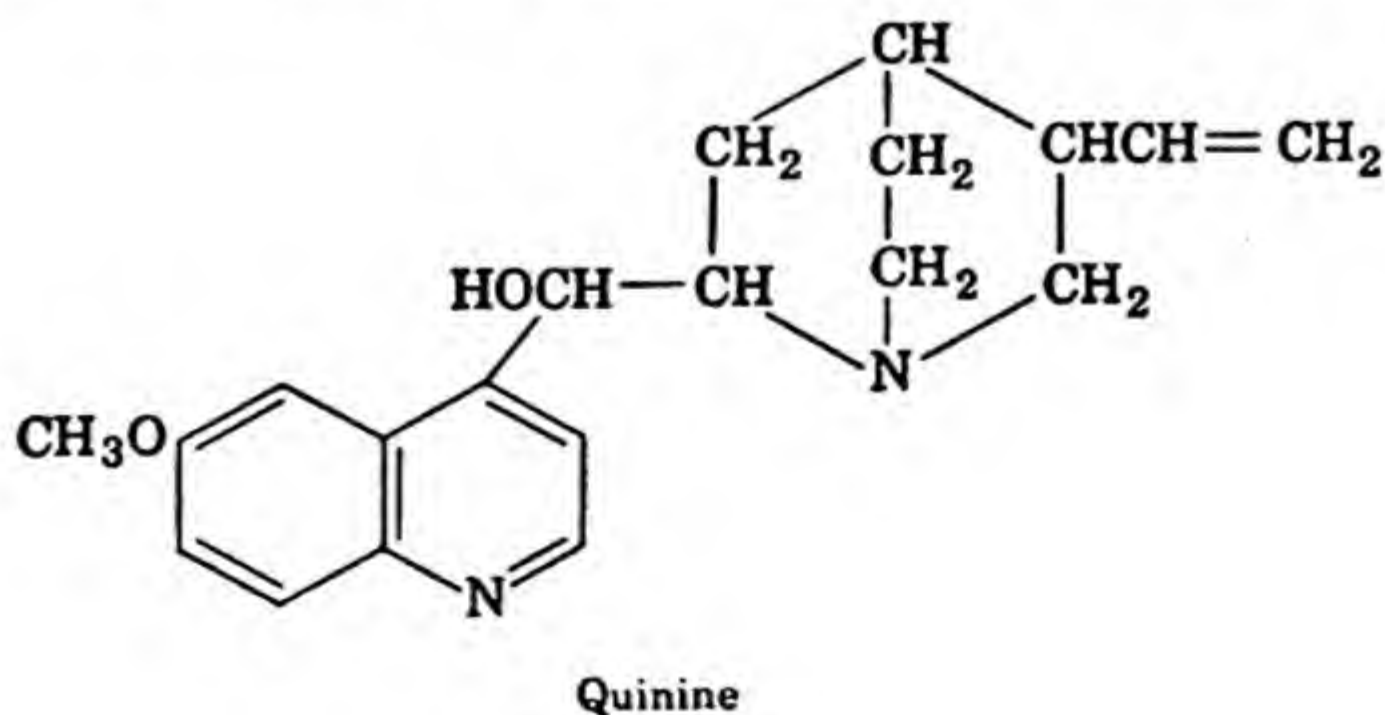


Cocaine and atropine, from coca leaves and belladonna, respectively, are tropane alkaloids. Although the structures of these two alkaloids are similar, their physiological effects are very different. Cocaine is a potent local anesthetic which is rather toxic and tends



to be habit-forming. It has been largely replaced by procaine (p. 192) and other synthetic drugs. Atropine is very toxic when ingested. Its sulfate in dilute solution is used to cause dilation of the pupil of the eye (mydriasis). Atropine and other belladonna alkaloids also cause relaxation of smooth muscle. Atropine is a racemic mixture; the levorotatory compound, also found in nature, is called hyoscyamine.

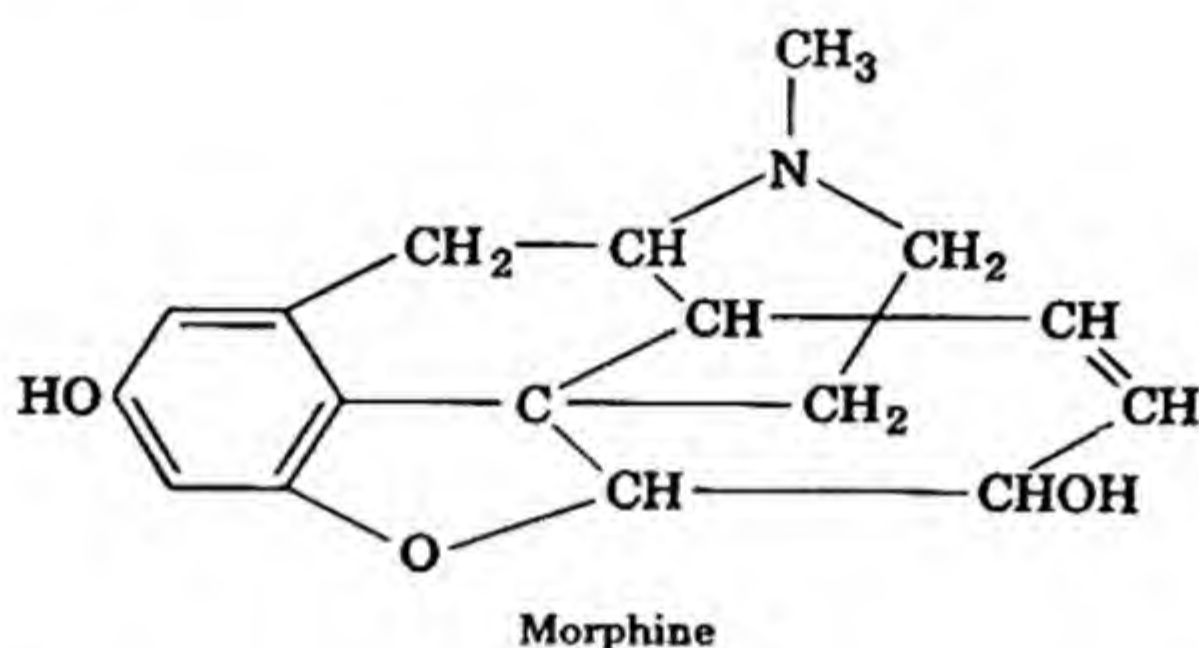
The best known of the quinoline alkaloids is quinine, which occurs in the bark of the cinchona tree with other alkaloids of similar structure. Quinine is an antipyretic and is used to lower body temperatures in the treatment of fevers, especially in malaria, the causative organism of which is attacked by the alkaloid. It is also used to some extent in beverages because of its bitter taste and to induce parturition. Quinine has largely been supplanted as an antimalarial by various synthetic substances (p. 258). It has been synthesized.



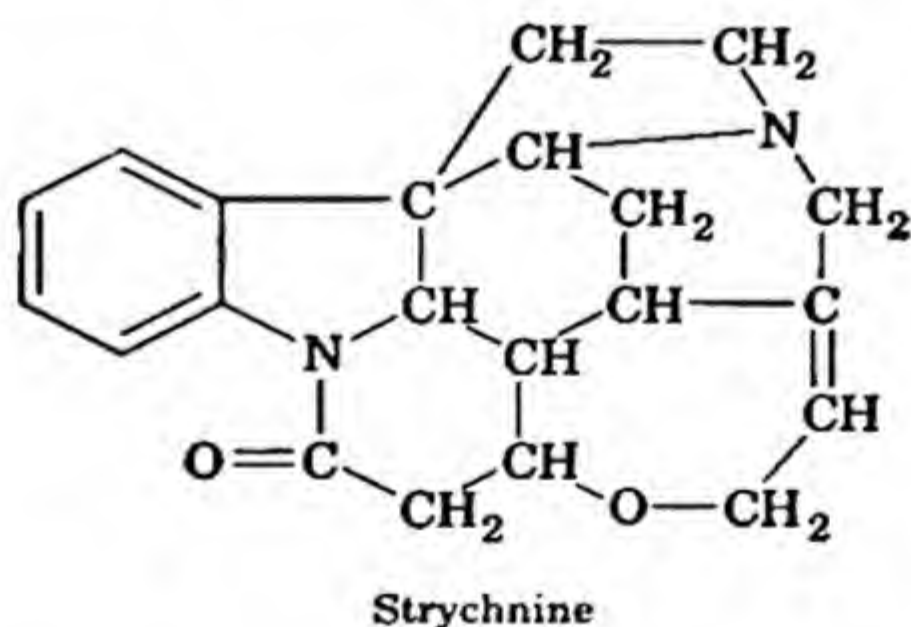
## Quinine



Opium is the dried latex of the opium poppy. It is a mixture of several alkaloids containing the quinoline and, in some cases, the phenanthrene ring systems, of which morphine and codeine are most familiar. Both are useful but habit-forming narcotics. Morphine sulfate is a potent analgesic; it is employed preoperatively and for patients in severe pain. Codeine, in which the phenolic hydroxyl group is methylated, is used in cough remedies and analgesic preparations. Heroin, in which both hydroxyl groups of morphine have been converted to acetates, is a dangerous drug because of its addiction tendency. On this account the manufacture or importation of heroin or its salts is forbidden in the United States.



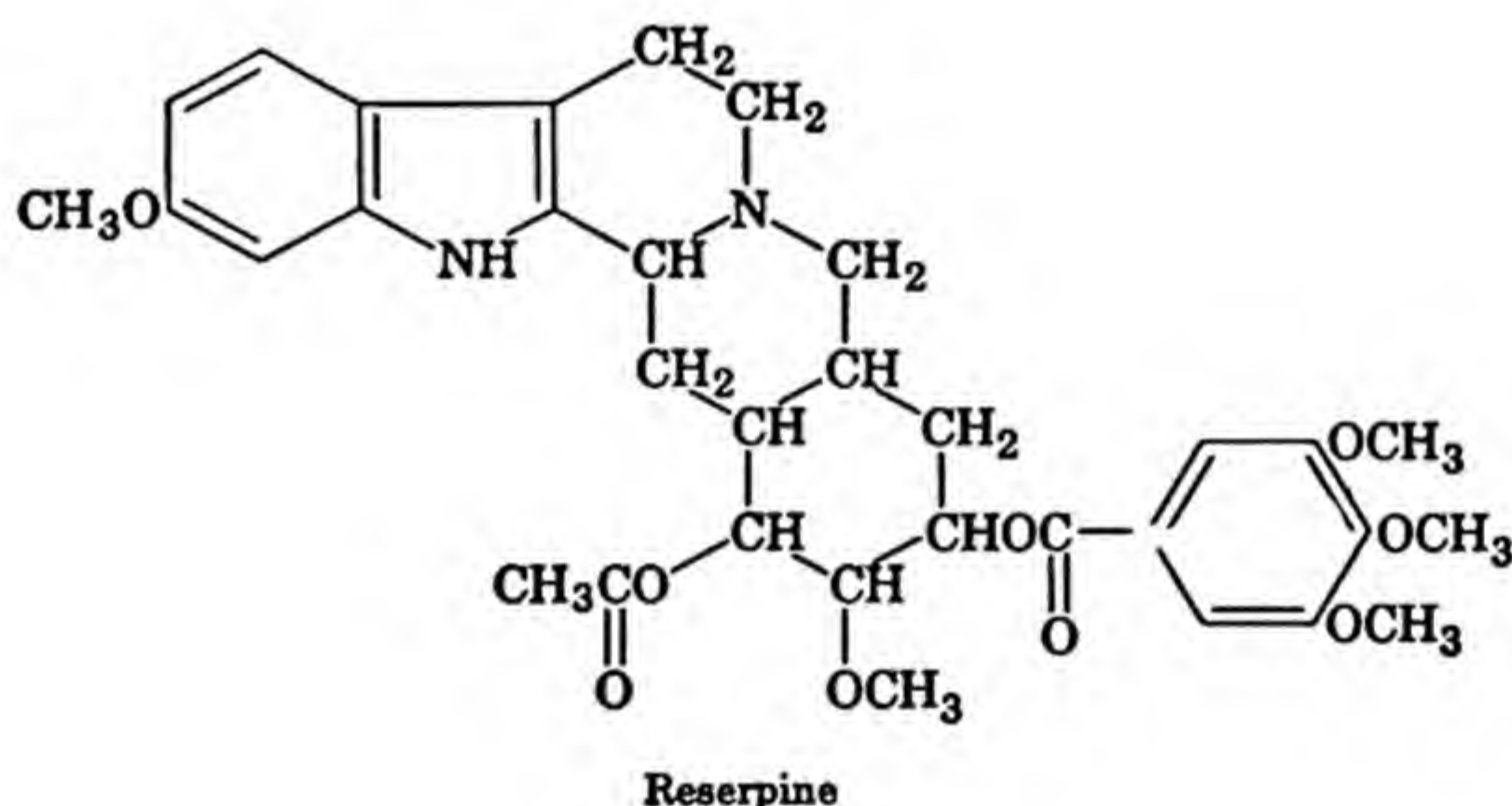
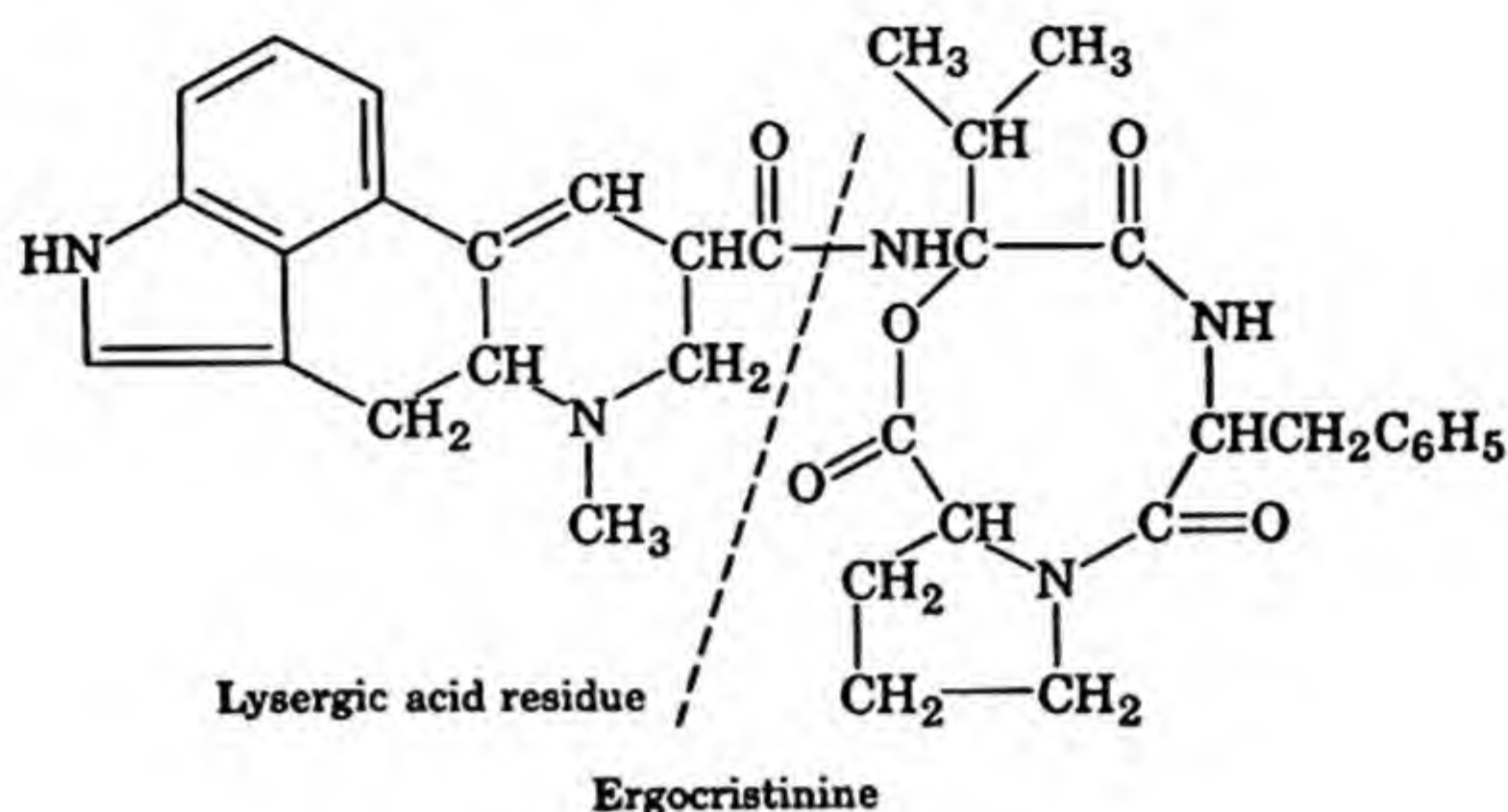
Among the most complex alkaloids are those containing the indole ring system. The structure of strychnine, from the seeds of the plant *nux vomica*, is known with certainty. Strychnine is a violent poison; it is used for exterminating rats and for trapping fur-bearing animals



but has the disadvantage of an extremely bitter taste. Ergot, a fungus that grows upon grain, particularly rye, is the source of a group of alkaloids used in medicine. These alkaloids are very toxic but, used in appropriate amounts, cause selective stimulation of the smooth muscle of the uterus. They are also employed in the treatment of migraine headaches for which they are specific. All of the ergot alkaloids are amides of lysergic or isolysergic acid, which are



optical isomers. The *Rauwolfia* alkaloids have come into prominence because of their tranquilizing properties and their ability to lower the blood pressure. An example is reserpine.

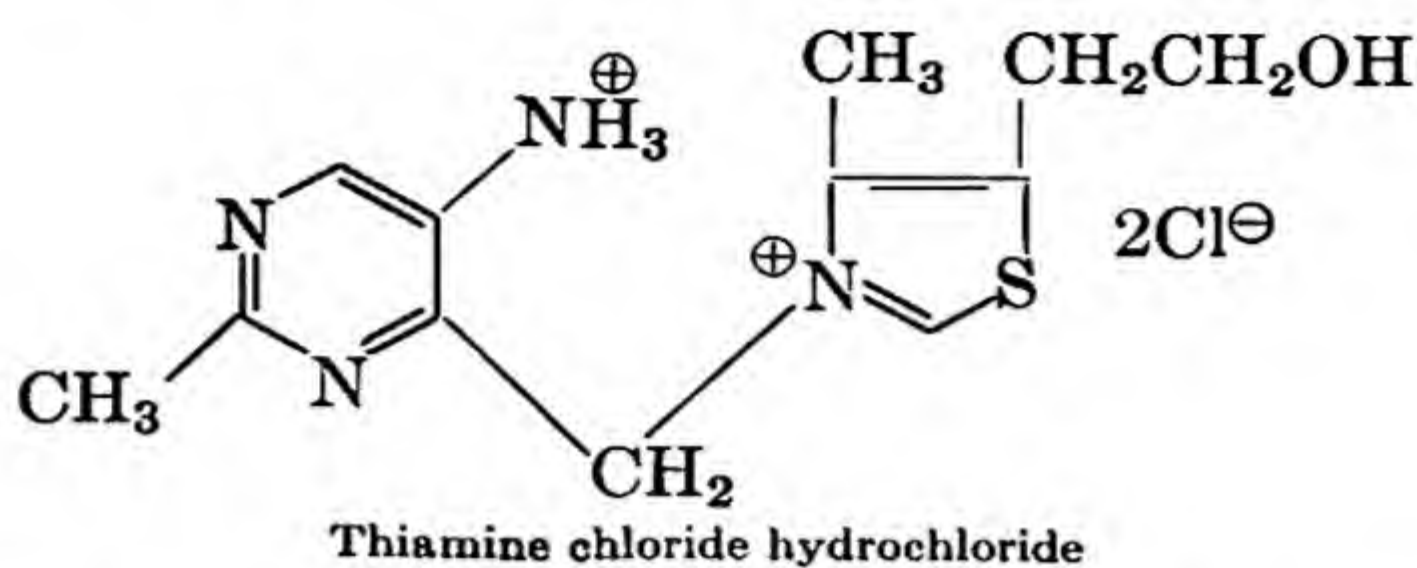


## ► VITAMINS

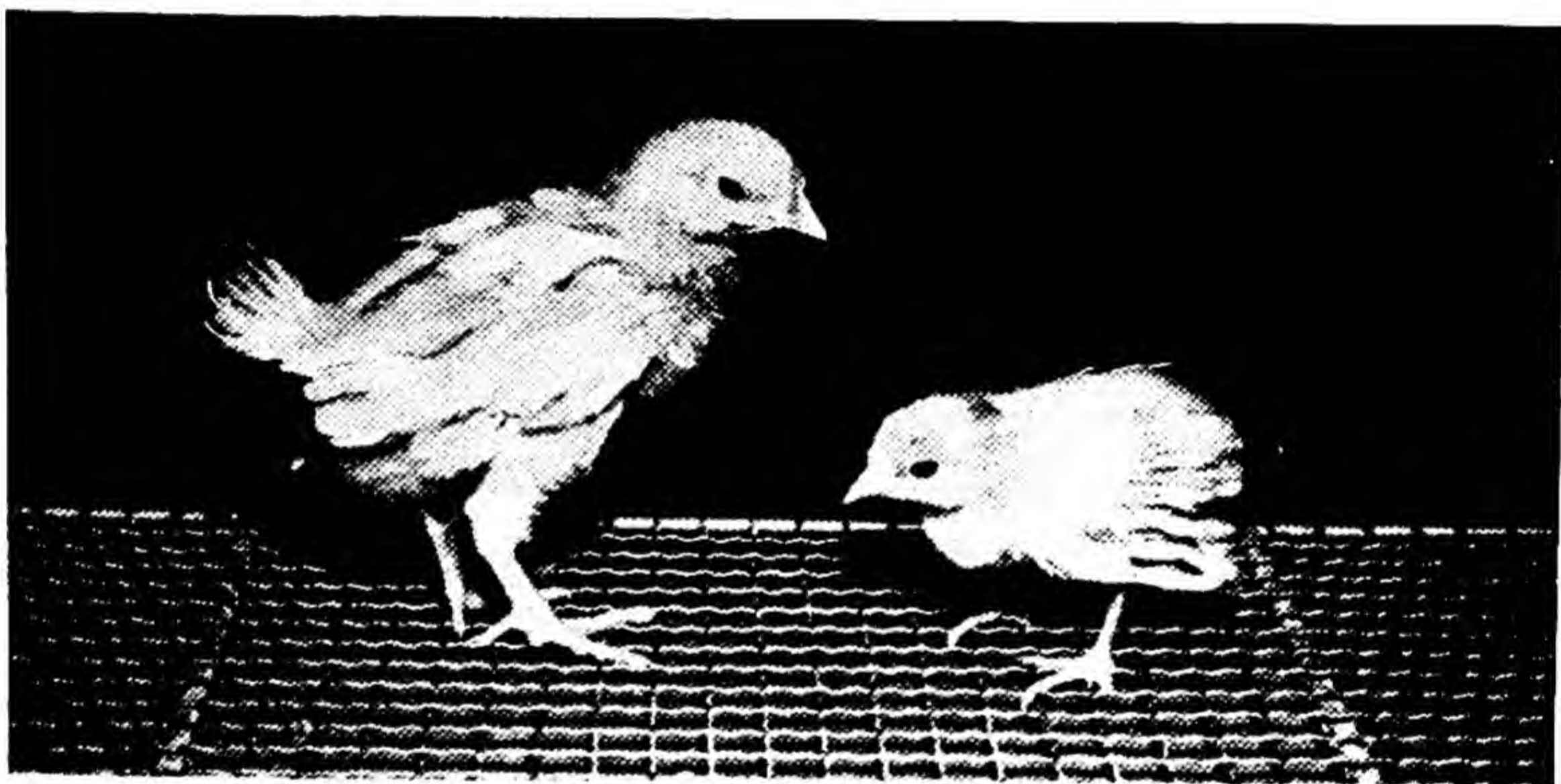
The B-vitamins form parts of the structure of the enzymes of the organism and thus are vitally concerned with metabolism. Most of the B-vitamins have heterocyclic rings, but nevertheless they are not closely related structurally.

The first member of the B-complex to be separated therefrom was thiamine, frequently known as vitamin B<sub>1</sub>. The collective symptoms of thiamine deficiency are called beriberi; there is no single obvious symptom. The victim suffers from nervous disorders, loss of appetite, gastrointestinal disturbances, fatigue, insomnia, and heart disturbances. Beriberi occurs most commonly in the Orient, where the diet consists largely of polished rice. Thiamine is a part of the

structure of various enzymes in the body which are involved chiefly in carbohydrate metabolism.



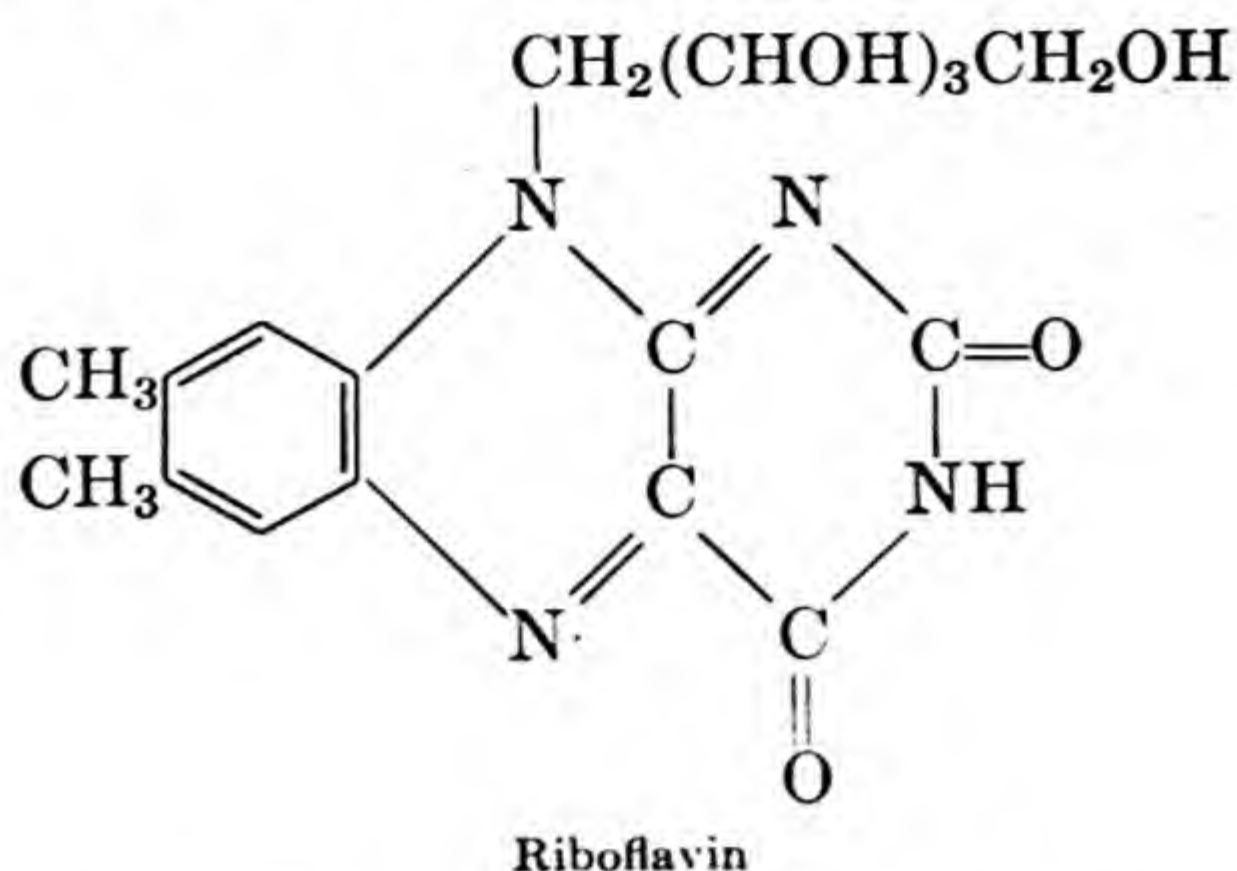
Thiamine contains a pyrimidine and a thiazole ring. In spite of its apparent complexity, the vitamin was the first to be synthesized on a commercial scale. It is of widespread occurrence in nature, but no one source has an especially high concentration.



Normal and riboflavin-deficient chicks. A deficiency of any of the B-vitamins in the diet results in retarded growth. There are no symptoms of riboflavin deficiency immediately recognizable as such. (Photograph courtesy of Merck and Company.)

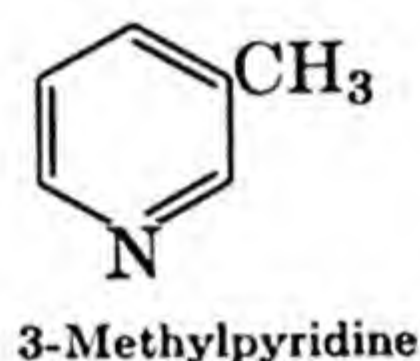
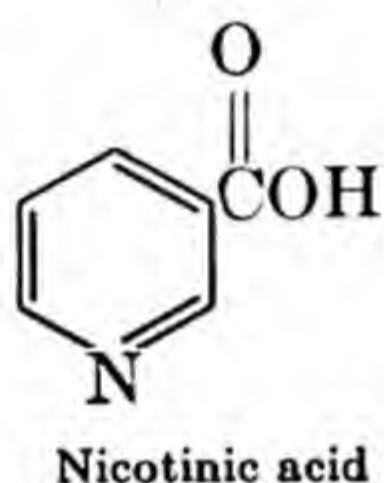
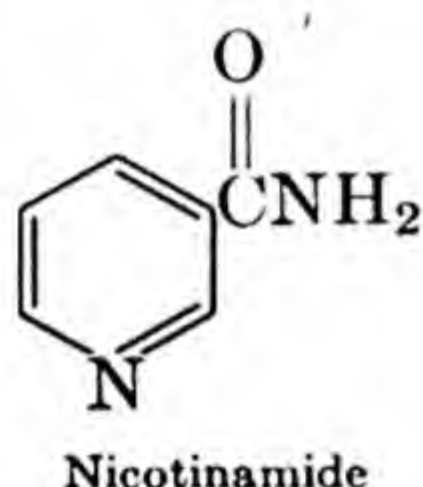
Riboflavin, originally known as vitamin B<sub>2</sub> or G, occurs in part of the structure of certain enzymes, important in biological oxidations. No definite deficiency disease is associated with riboflavin. The tongue becomes inflamed, and sores appear in the corners of the mouth. There is usually a dermatitis, and the eyes may be affected. Nearly always, however, riboflavin deficiency is accompanied by deficiencies of other B-vitamins.





Riboflavin is a yellow-orange solid, rather stable toward heat but not light. It contains a D-ribityl group derived from the pentose, D-ribose. The three-ring system present in riboflavin is known as the isoalloxazine system.

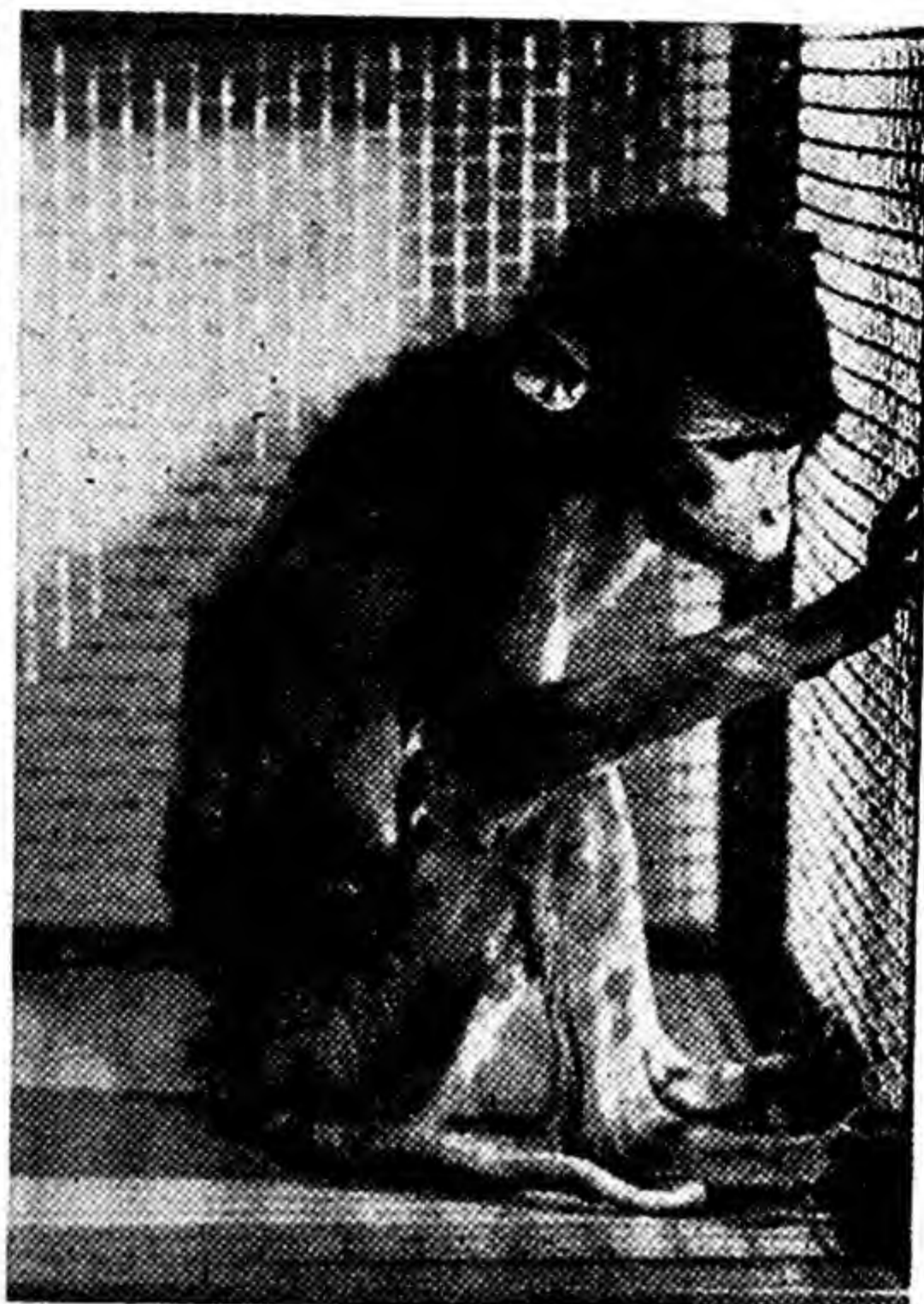
Nicotinamide is structurally the simplest vitamin. Both nicotinic acid and the amide have vitamin properties, and both occur naturally.



The acid can be obtained by the oxidation of  $\beta$ -picoline (3-methylpyridine), or nicotine or quinoline (p. 240) followed by decarboxylation. The typical deficiency disease associated with nicotinamide is pellagra. However, sometimes cures are not effected by nicotinic acid or the amide, and other B-vitamins are needed as well. It is sometimes said that the symptoms of pellagra are dementia, diarrhea, and dermatitis. The tongue also becomes red and inflamed. A nicotinic acid residue is contained in triphosphopyridine nucleotide and diphosphopyridine nucleotide, present in enzymes which catalyze dehydrogenation in carbohydrate metabolism.

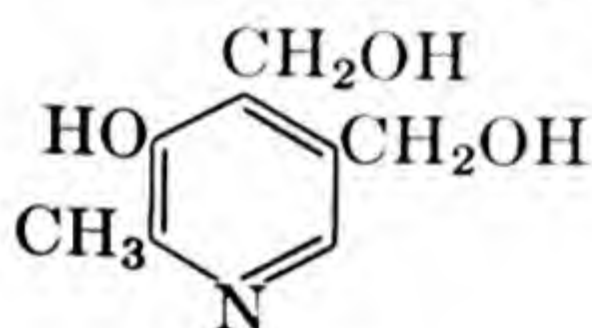
Pyridoxine (vitamin B<sub>6</sub>), like nicotinic acid, is a pyridine derivative. No clinical symptoms of pyridoxine deficiency have been noted in adult man, though convulsive disorders have been observed in infants on a B<sub>6</sub>-deficient diet. The symptoms seen in certain experimental animals are much like those of biotin-fatty acid deficiencies. Rats, for example, develop a severe dermatitis of the extremities. They and other animals may also develop nervous disorders and anemia. Pyridoxine may be replaced by pyridoxamine or pyridoxal in the diet. All three occur naturally, but pyridoxal appears to be the



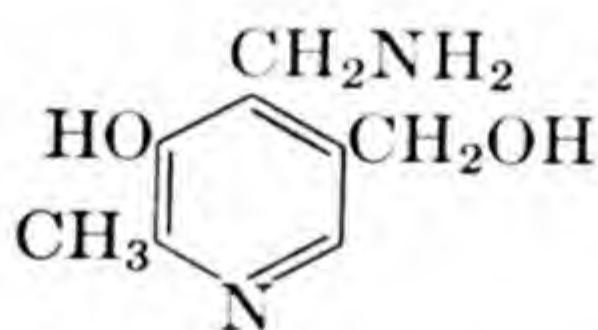


Normal and pyridoxine-deficient monkey. A result of insufficient pyridoxine is the much sparser growth of fur, which is especially noticeable in the tail. (Photograph courtesy of Merck and Company.)

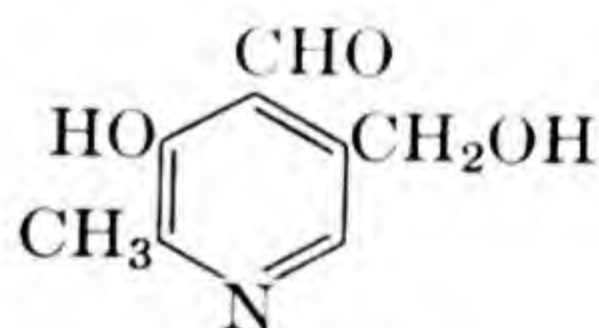
compound present in enzymes which catalyze various reactions involving amino acids.



Pyridoxine

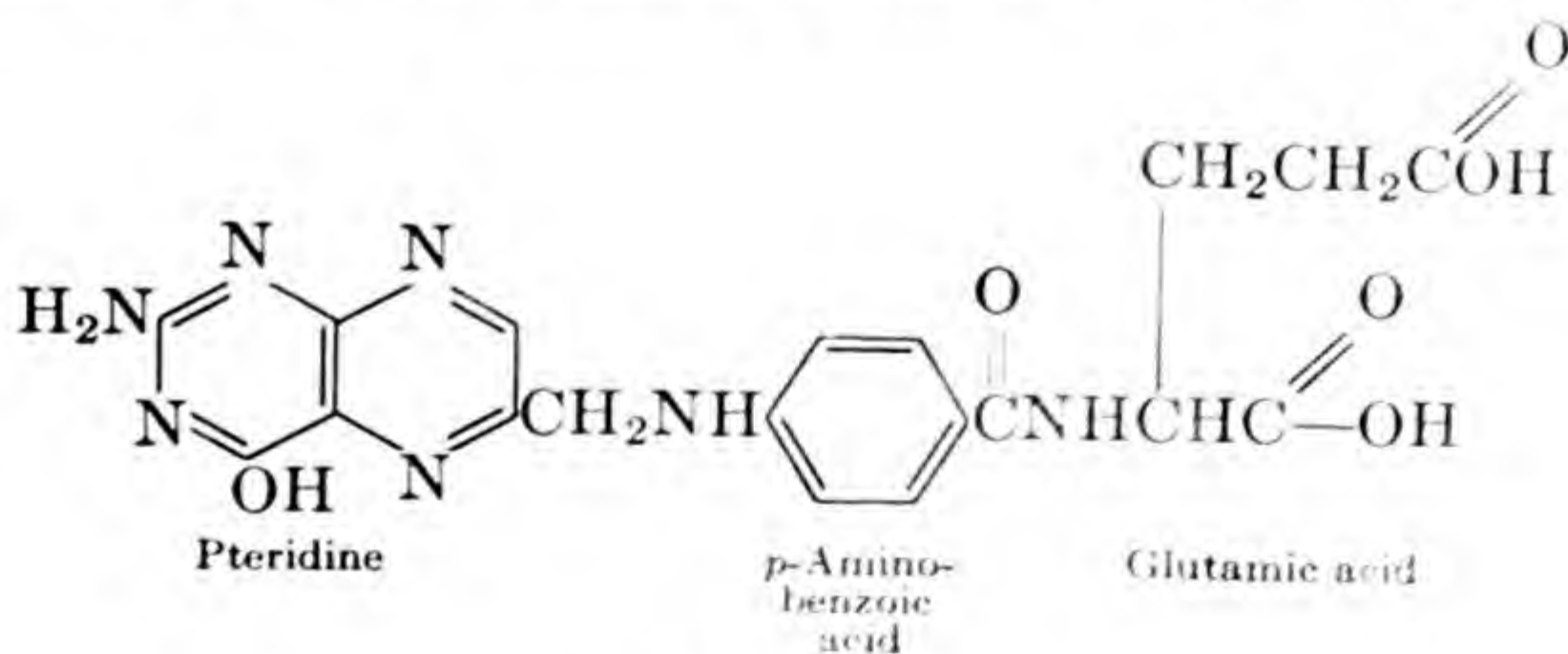


Pyridoxamine



Pyridoxal

Folic acid, the structure of which is shown here, has the pteridine ring system and a *p*-aminobenzoic acid residue. A number of substances having similar structures also have similar biological activity.

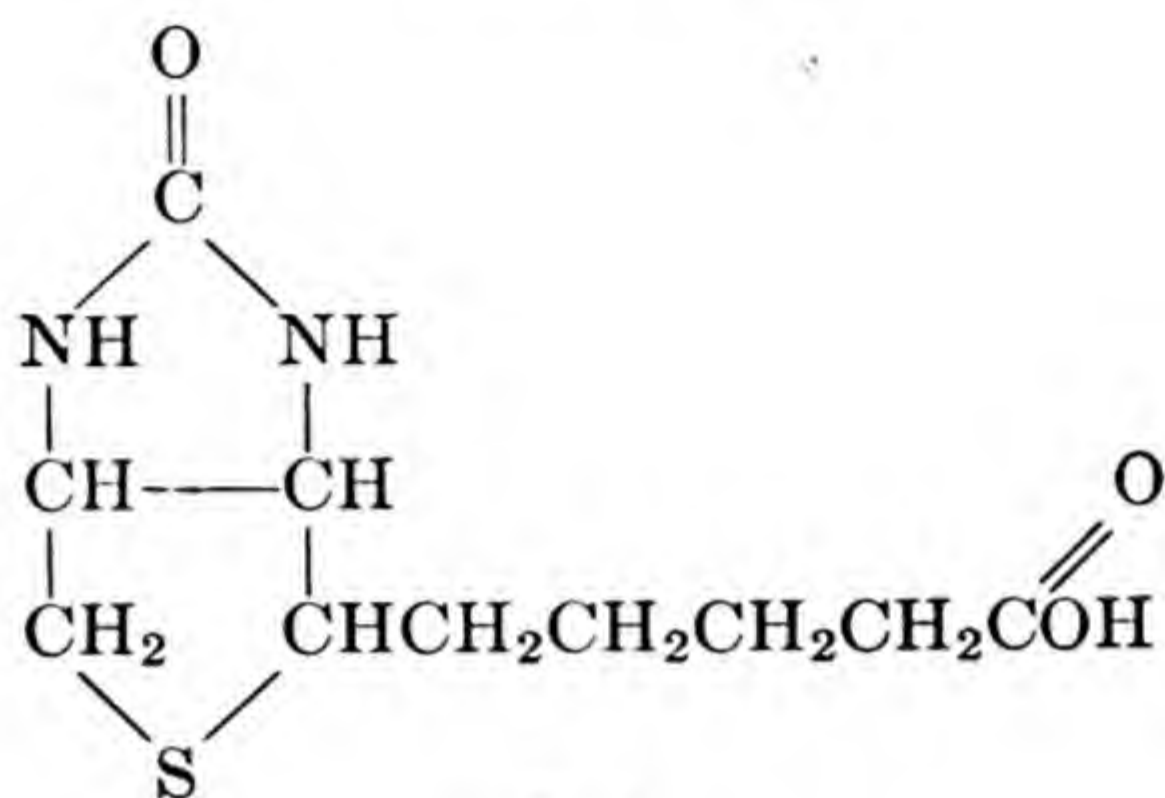


**Folic Acid**



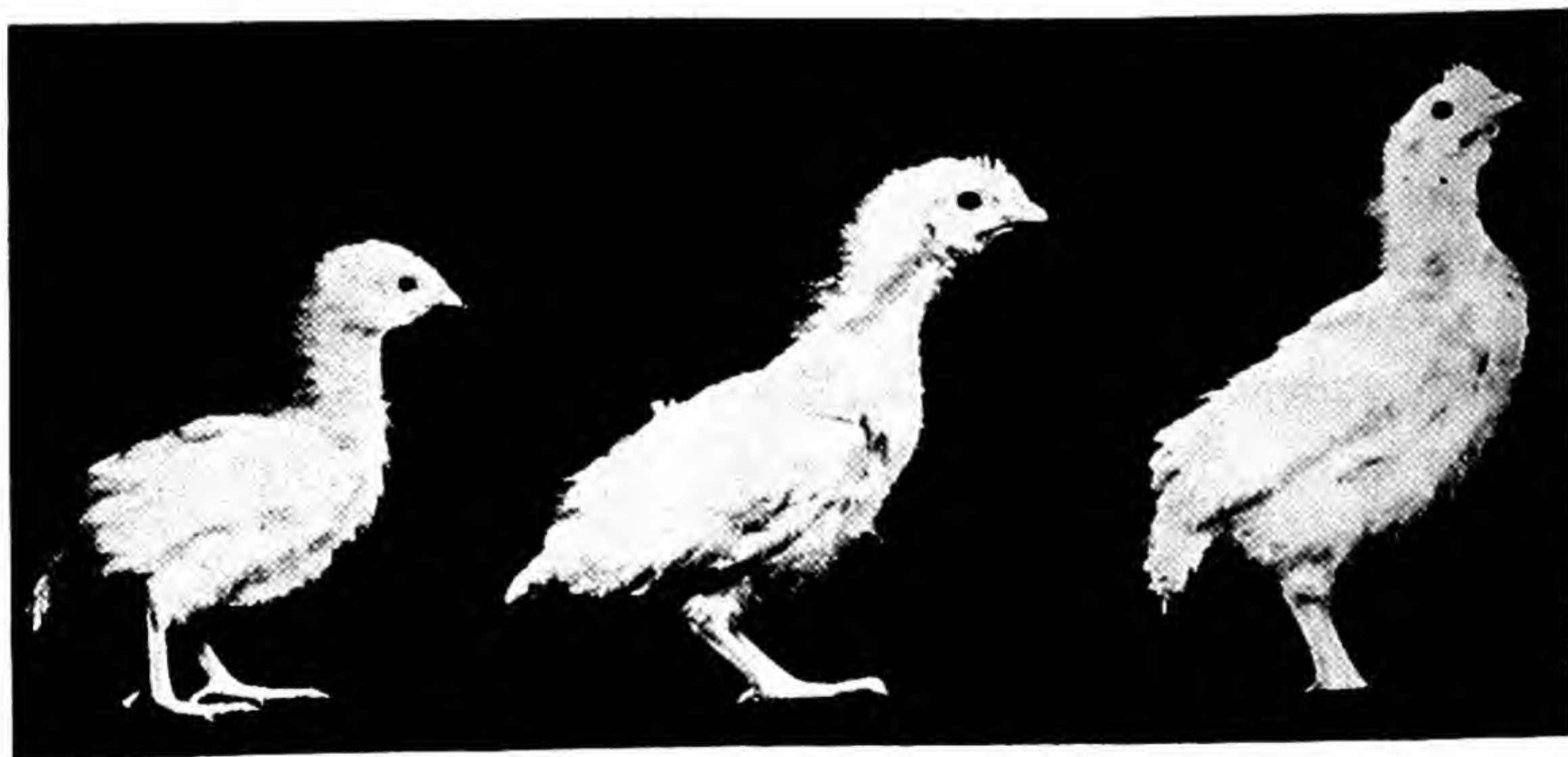
Folic acid is probably an essential constituent of the diet of man, though deficiency diseases are difficult to produce because microorganisms in the host are capable of synthesizing it. A deficiency of folic acid leads to anemia in chicks and graying of hair in rats.

Biotin has two five-member rings which are condensed, an uncommon arrangement in nature. True biotin deficiencies are difficult if not impossible to produce in animals because the microorganisms of the intestines are able to synthesize it. However, symptoms can be



Biotin

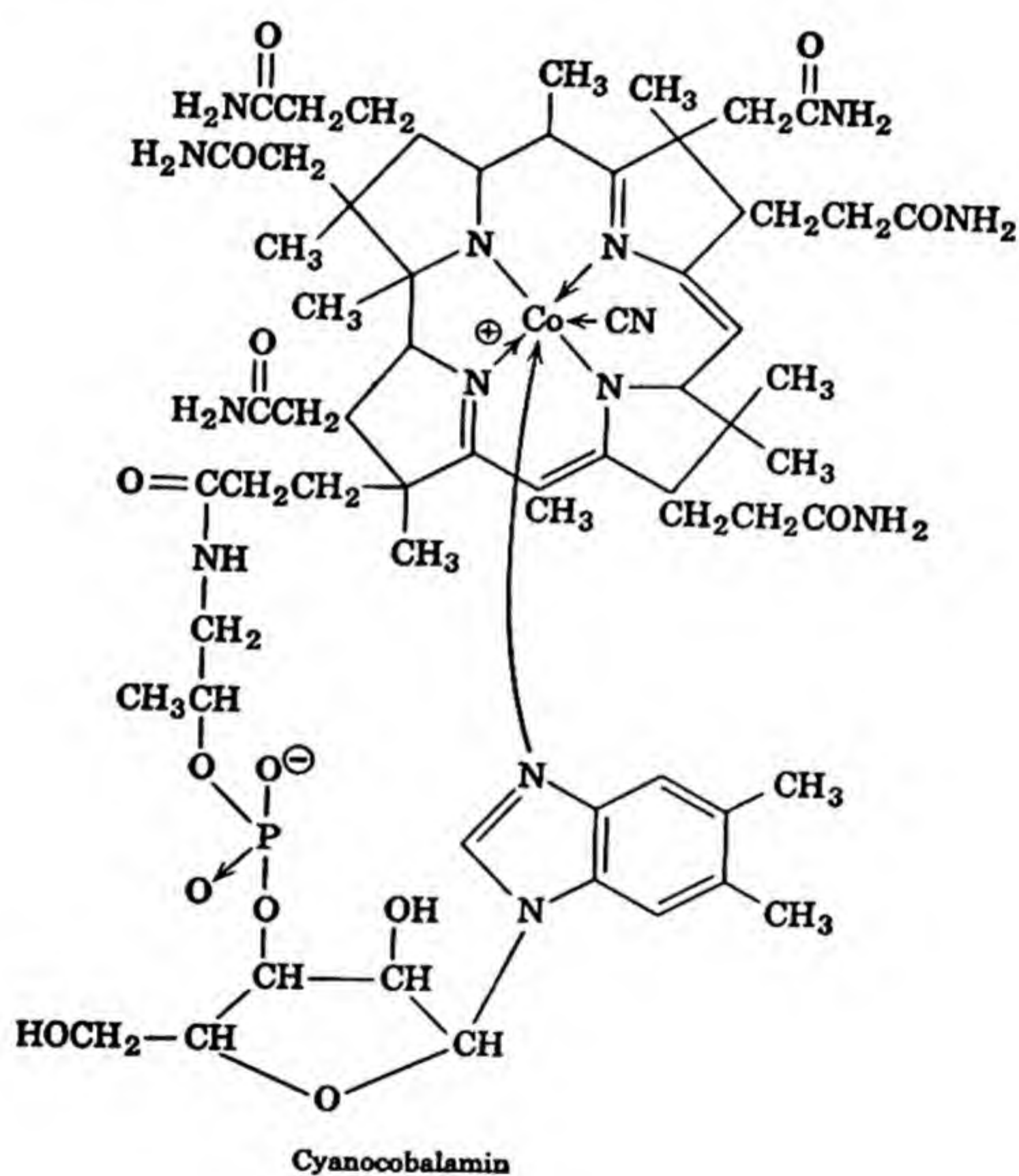
caused in experimental animals and man by feeding them large quantities of raw egg-white which contains avidin, a protein which combines with biotin in such a way that the vitamin is difficult to divorce from it. In man restlessness, nervous disorders, dermatitis, and hallu-



The effect of vitamin B<sub>12</sub> on the growth of chicks. The diet of the chick on the left contained no B<sub>12</sub>, that in the center, an inadequate amount, and that on the right, the needed amount for normal growth. (Photograph courtesy of Merck and Company.)

cinations occur. Symptoms are eliminated when biotin or oxybiotin (in which the sulfur is replaced by oxygen) is administered.

Cyanocobalamin, Vitamin B<sub>12</sub>, appears to be required by animals and man for normal growth. Deficiency of it produces anemias curable by the administration of the vitamin, sometimes orally, sometimes by injection. Extremely small amounts of the vitamin have a significant effect. For example, noteworthy improvement in anemias has been produced with as little as 1 microgram (0.000001 gram). The structure proposed for this vitamin is of much interest because of its great complexity and because of its unusual structural features. For example, the cobalt, cyanide, and benzimidazole ring system occur very uncommonly in nature.

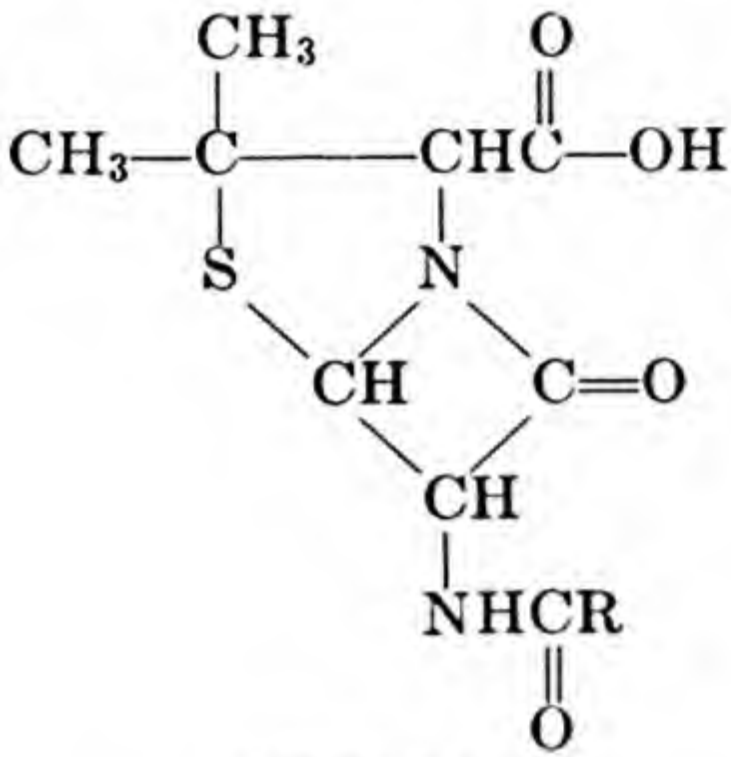


## ► ANTIBIOTICS

Some of the antibiotics, notably the penicillins, contain heterocyclic rings. There are at least six closely related compounds produced by various molds of the *Penicillium* type. Isolation of the penicillins is difficult because of their instability and because of their low con-



centration in the culture medium. However, these difficulties have been overcome, and manufacture of the penicillins is carried out on a large scale.

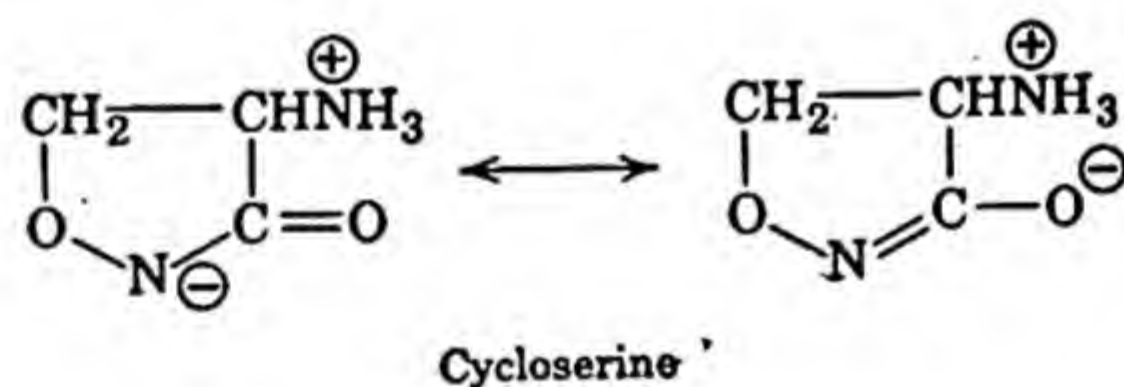
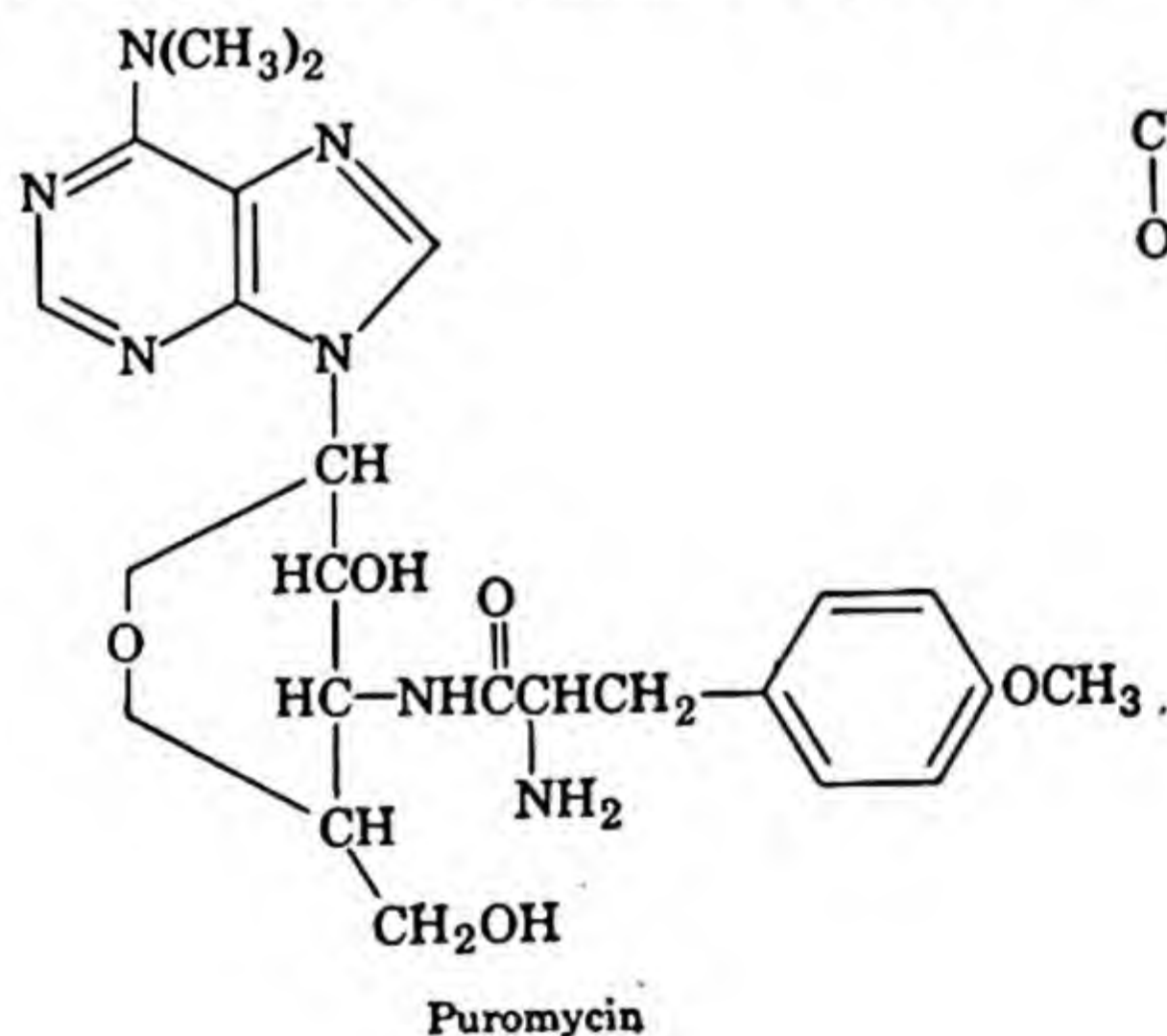
	Type	R
	Benzylpenicillin	$-\text{CH}_2\text{C}_6\text{H}_5$
	Hydroxybenzylpenicillin	$-\text{CH}_2\text{C}_6\text{H}_4\text{OH}$
	Amylpenicillin	$-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$
	Pentenylpenicillin	$-\text{CH}_2\text{CH}=\text{CHCH}_2\text{CH}_3$
	Heptylpenicillin	$-\text{CH}_2(\text{CH}_2)_5\text{CH}_3$
	Phenoxymethylpenicillin	$-\text{CH}_2\text{OC}_6\text{H}_5$

Penicillins

The types of penicillin differ only in the nature of the R group. Amyl, phenoxymethyl, and benzylpenicillins are those most commonly employed. The ring system in the penicillins is unusual in that it is composed of a four- and a five-membered ring condensed together.

The penicillins have been synthesized in such a way that the R group can be varied within very wide limits. It is thus possible to prepare penicillins that do not occur in nature.

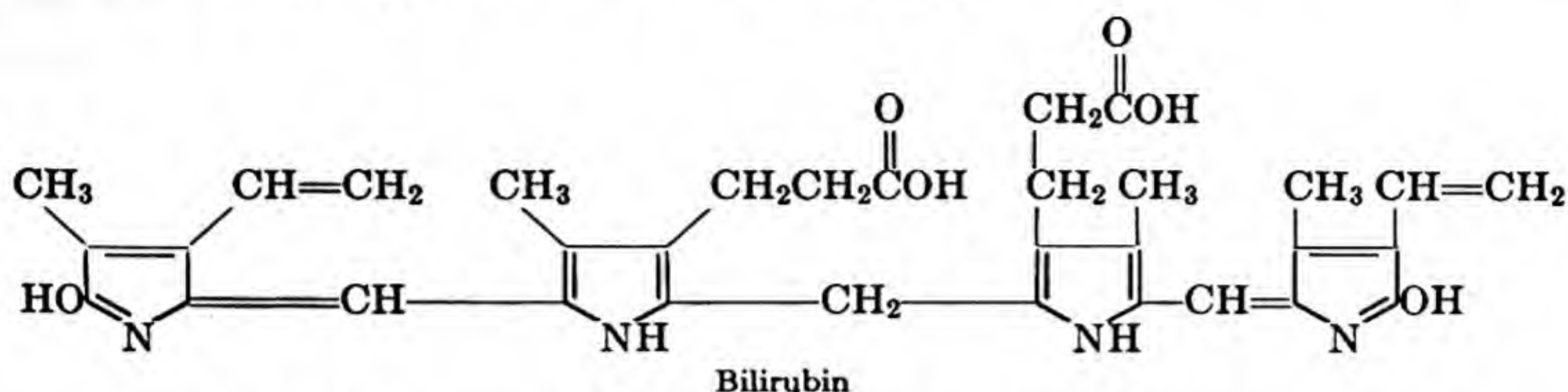
Two other antibiotics containing heterocyclic rings are puromycin and cycloserine. Puromycin has a purine ring system. Cycloserine (Oxamycin) is a rather simple molecule, but one which is best represented as a resonance hybrid.



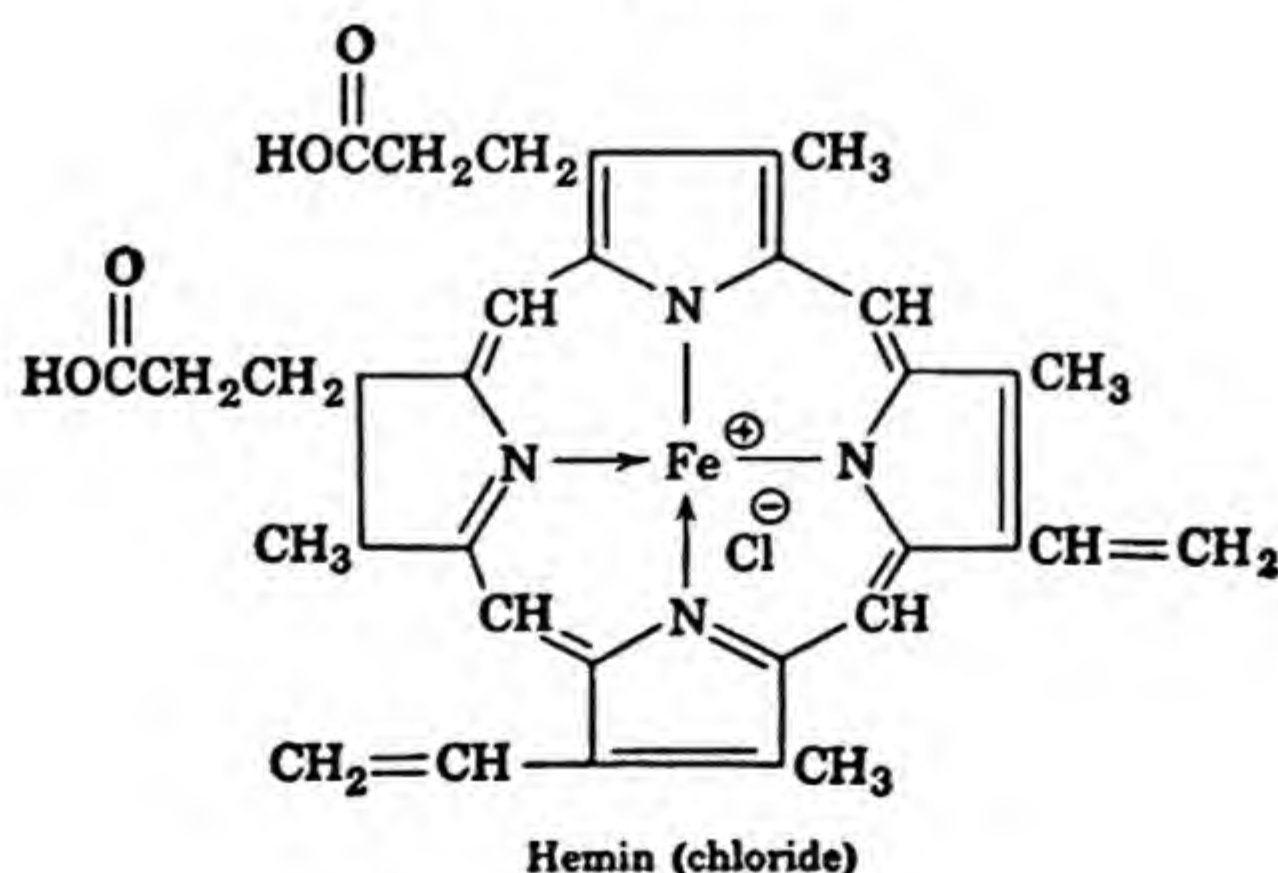
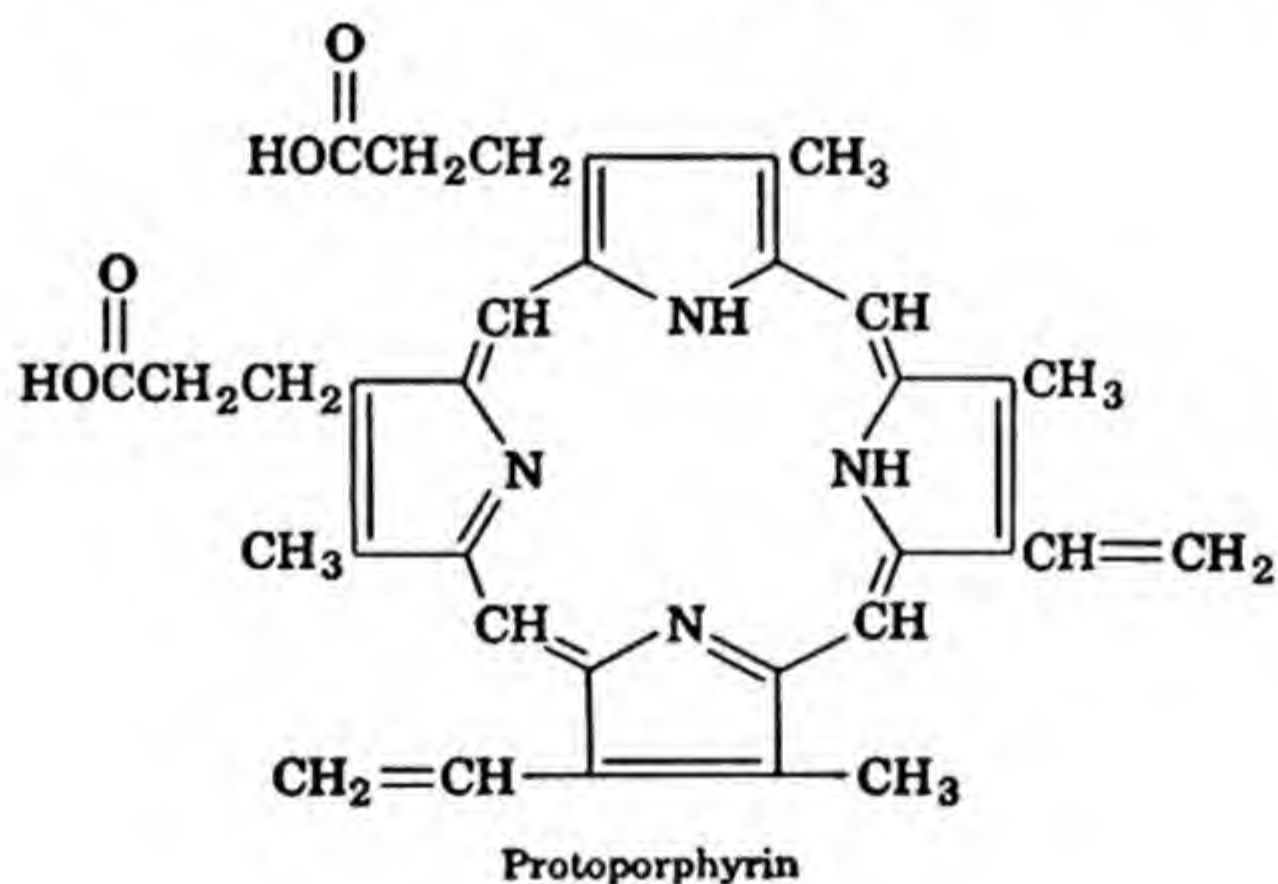
## ► OTHER NATURALLY OCCURRING COMPOUNDS

Among the numerous other heterocyclic compounds that occur in nature those containing four pyrrole (or reduced pyrrole) nuclei are

especially important. They include the bile pigments, of which bilirubin is an example, hemin, and chlorophyll.



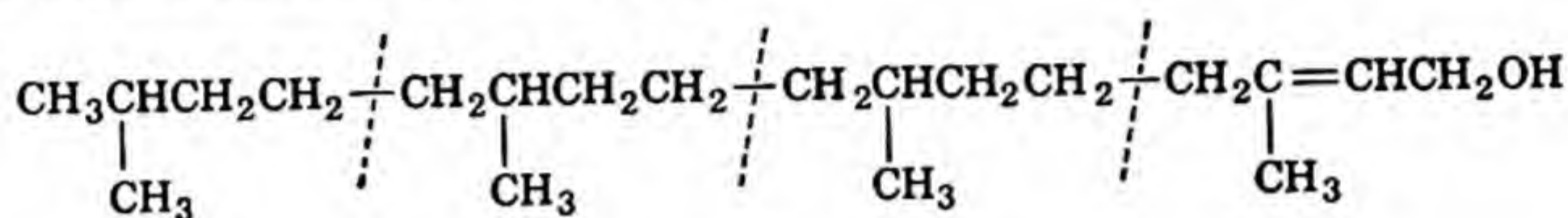
In certain of the pyrrole pigments the heterocyclic nuclei are associated with metals. Hemoglobin, for example, is a chromoprotein in which the colored part of the molecule contains four pyrrole rings linked to an iron atom. Careful hydrolysis of hemoglobin yields the protein (a globin) and the pigment ferrohemin. If oxygen is available, the iron is oxidized to the ferric state to yield the pigment hemin. The iron may be removed from hemin by the action of an acid reducing agent. The iron-free pigment is called protoporphyrin, and its structure has been confirmed by synthesis. It is an example of the class of pigments known as porphyrins, which are characterized



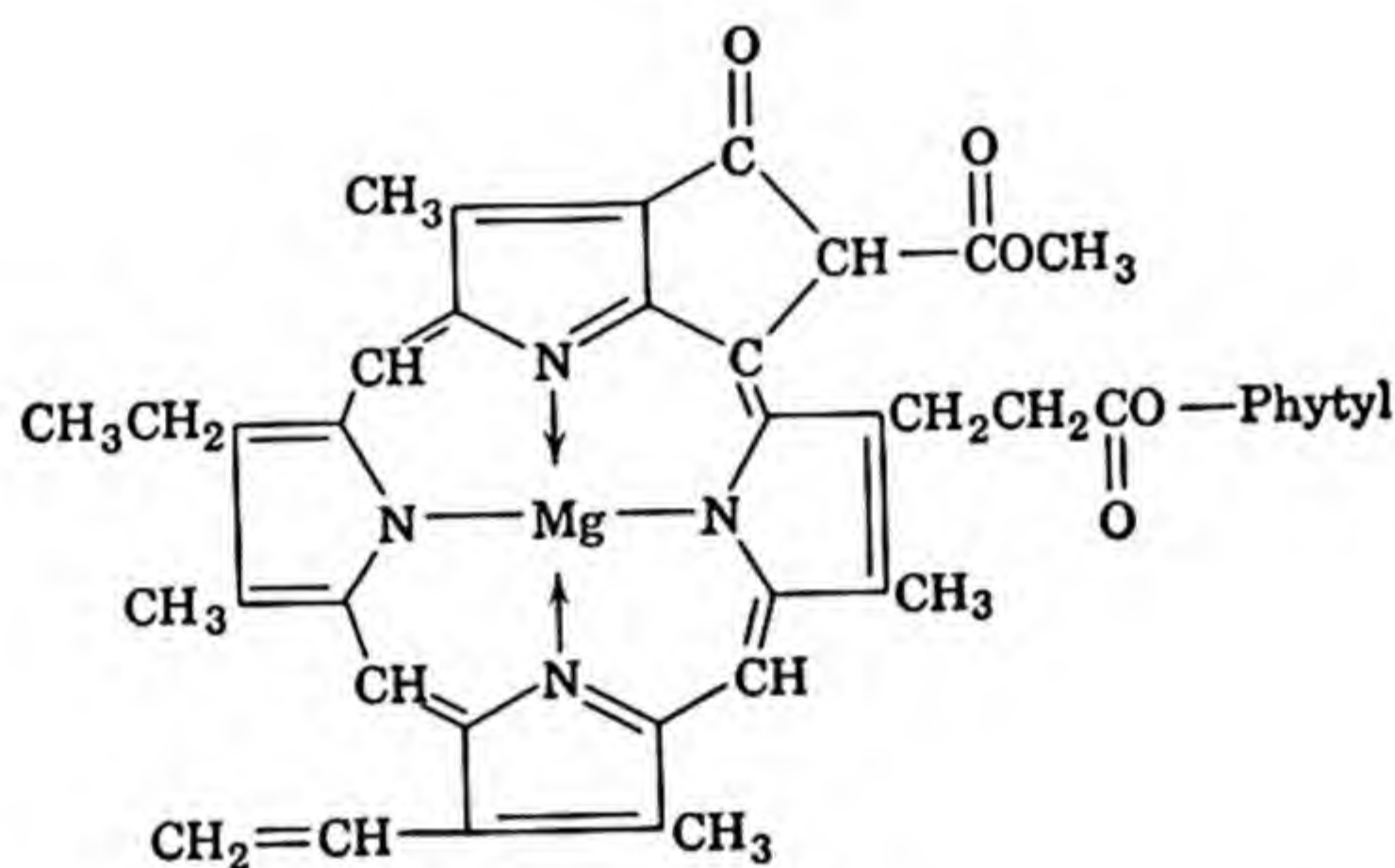


by four pyrrole nuclei joined in a ring by four methine groups ( $-\text{CH}=\text{}$ ).

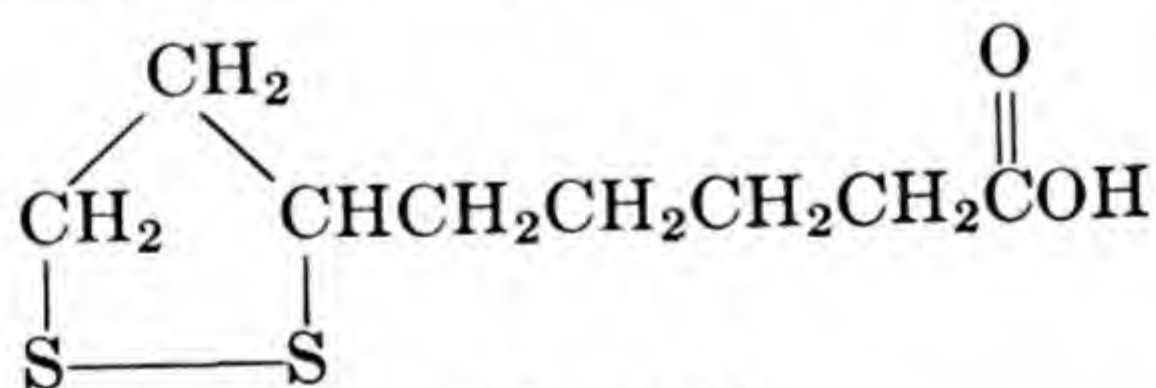
The chlorophylls, or green pigments of plants, are also pyrrole derivatives. Their skeletal structure is more complex, and they contain magnesium instead of iron. The two chlorophylls (*a* and *b*) differ in that the latter possesses an aldehyde group in place of one of the methyl groups. They are both esters of dibasic acids and upon hydrolysis give methanol and phytol.



Phytol

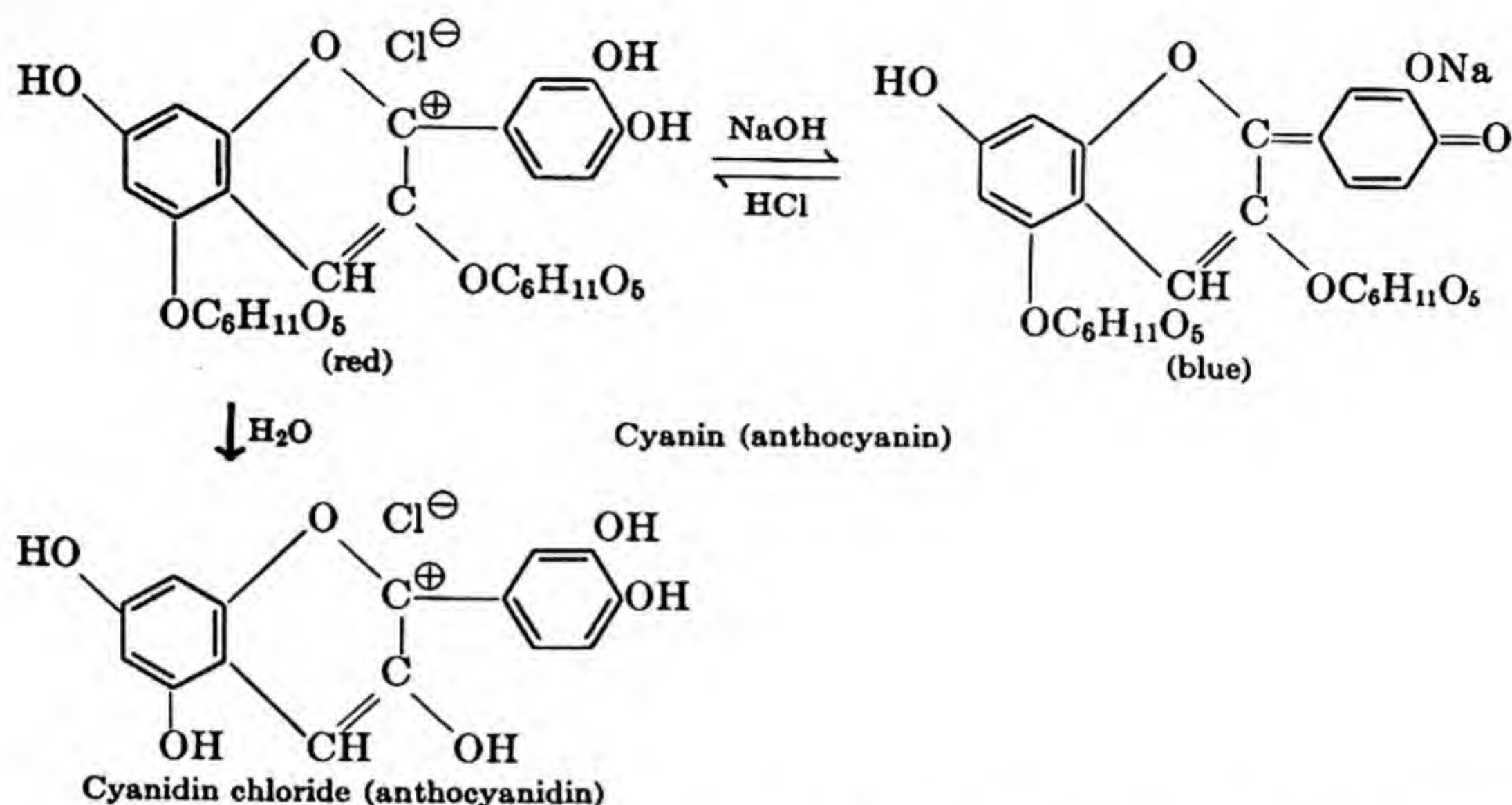
Chlorophyll *a*

Chlorophyll is vital in the photosynthetic process. Other substances are involved, such as  $\alpha$ -lipoic acid (thioctic acid).

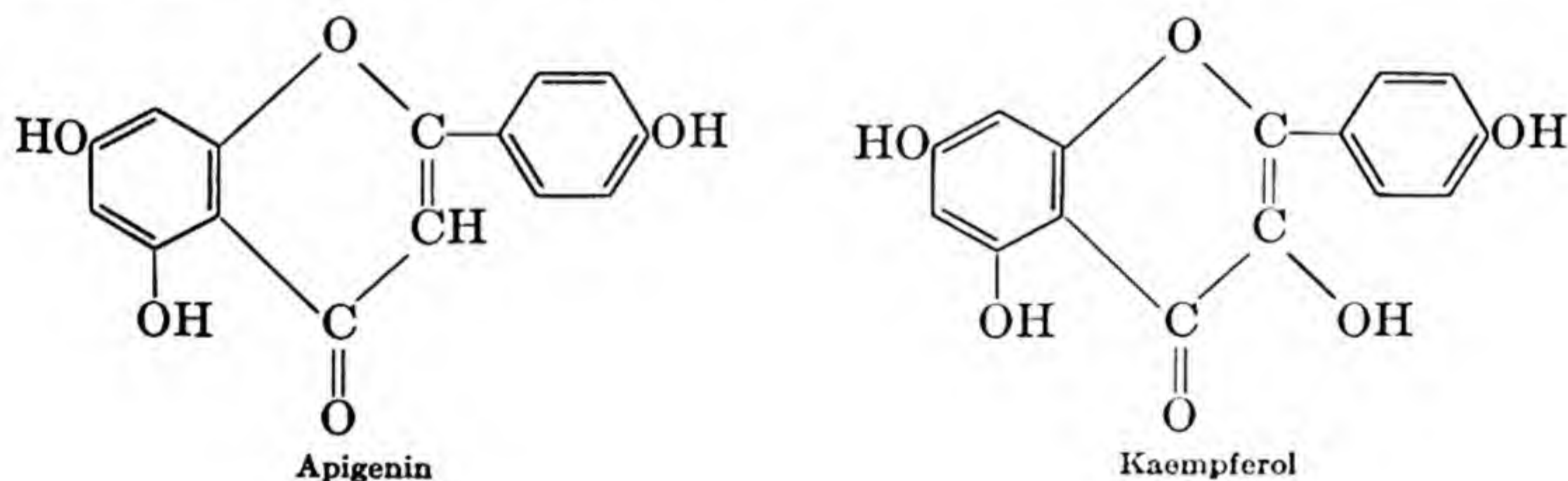
 $\alpha$ -Lipoic acid

Many plant pigments have oxygen-containing heterocyclic rings. They belong to two closely related groups of compounds, the anthocyanins and the flavones. The anthocyanins are glycosides and are generally found in solution in the cell sap. Anthocyanins undergo a change in chromophoric group in going from acid to basic conditions. In acid solution the pigment probably exists as a salt. The structure of cyanin, a typical anthocyanin, is indicated below. In basic solution a change in the structure occurs, and one of the rings becomes quinoid. A change of color results; in this property the anthocyanins

resemble indicators. Thus cyanin can be responsible for the blue of the cornflower and the red of the rose.



The flavones are widely distributed yellow pigments which sometimes occur uncombined and sometimes as glycosides. Flavones having a hydroxyl group in the heterocyclic ring are known as flavonols. The structural formulas of a flavone and a flavonol are shown here. Apigenin occurs in parsley and the yellow dahlia, and kaempferol in the flowers of the blue delphinium.



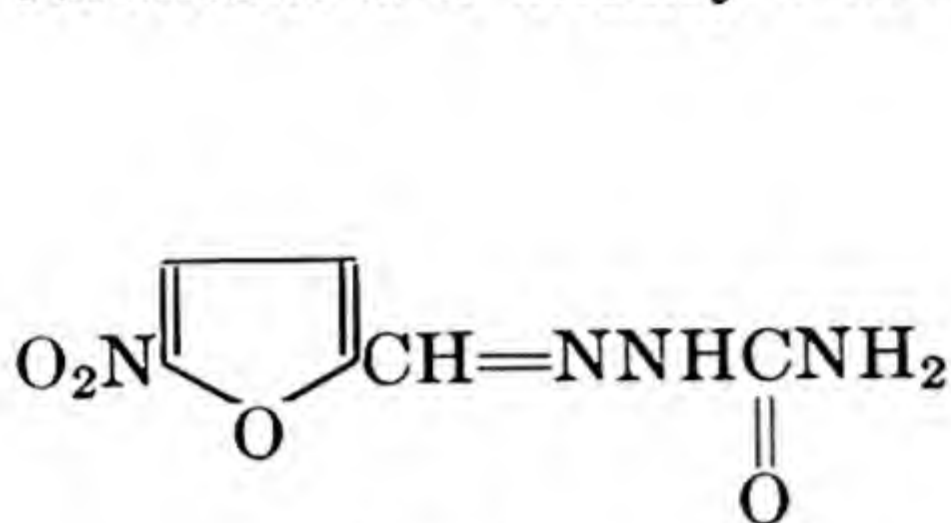
## ► SYNTHETIC COMPOUNDS OF COMMERCIAL VALUE

Heterocyclic compounds have assumed an increasing importance, particularly in the medicinal field. We shall consider only a few such compounds, with emphasis on variety of structure as well as application.

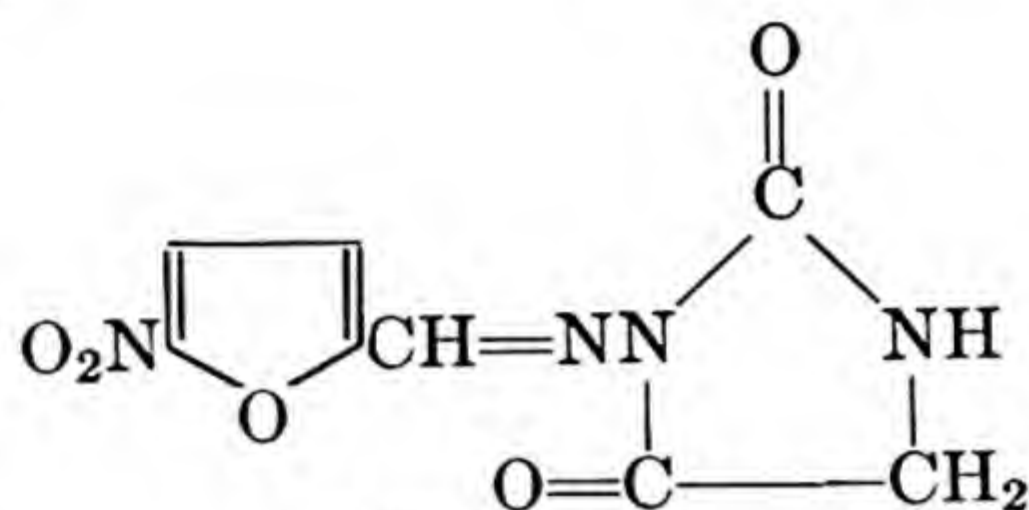
Certain furan compounds have proved effective as anti-infective agents. Two derivatives of 5-nitrofurfural, nitrofurazone and nitro-



furantoin, are examples. Nitrofurazone is employed in external infections and as a protective compound in burns and surgery. Nitrofurantoin is a urinary tract antiseptic.

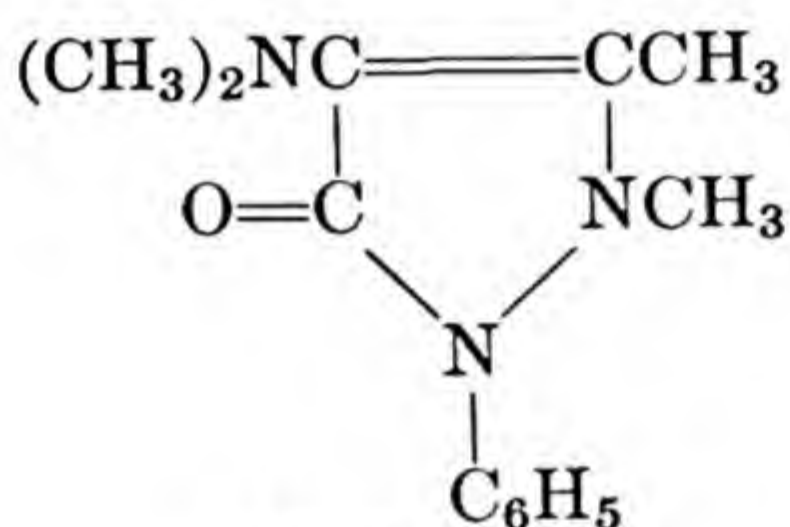


Nitrofurazone

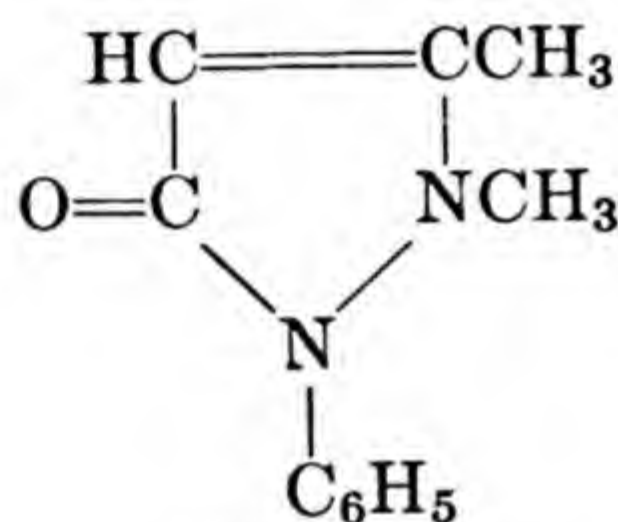


Nitrofurantoin

Pyrazole derivatives have long been employed in medicine as analgesics and antipyretics. Aminopyrine and antipyrine are examples.

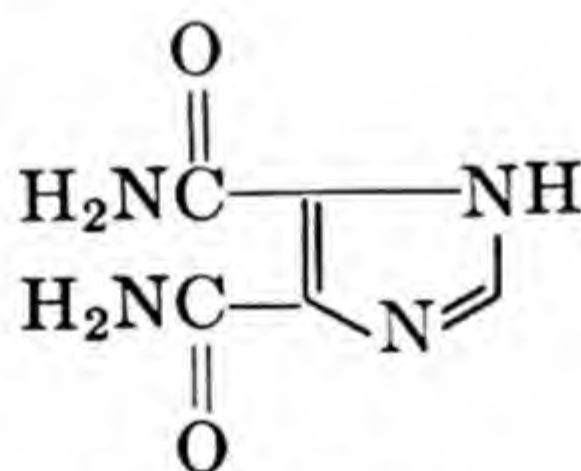


Aminopyrine



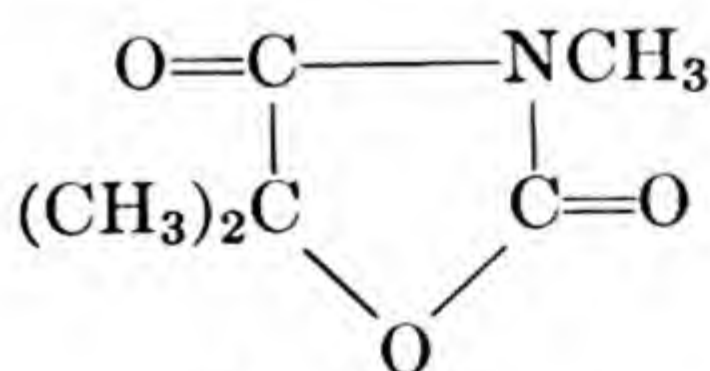
Antipyrine

Glycarbylamide, an imidazole derivative, is incorporated into fowl feeds as a coccidiosis preventive.

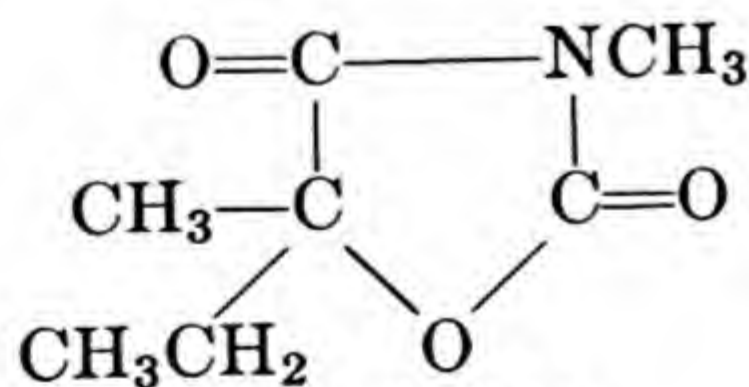


Glycarbylamide

Oxazole derivatives have found application in the treatment of epilepsy. Trimethadione and paramethadione are often effective in reducing the frequency and severity of seizures in *petit mal*.

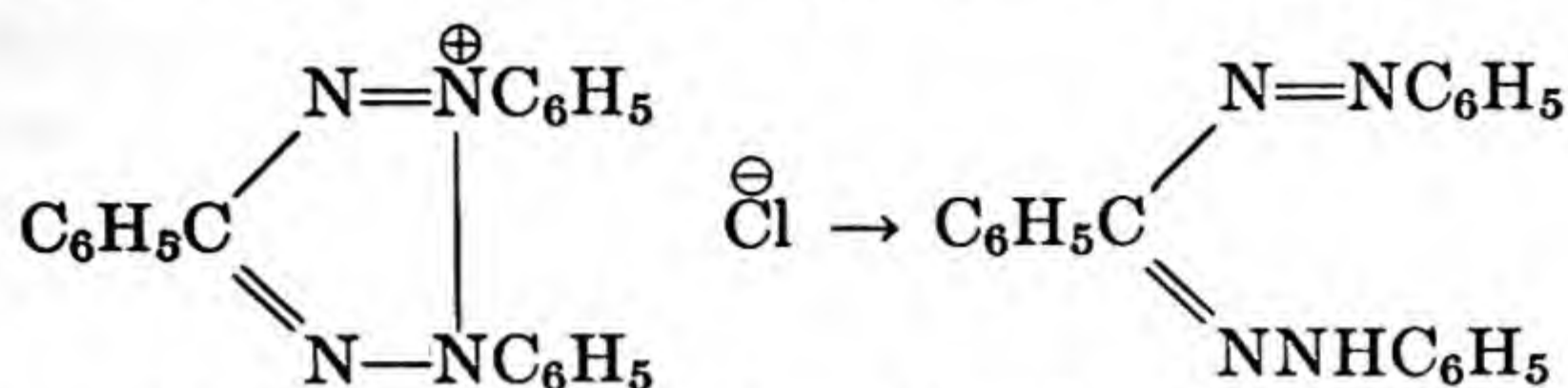


Trimethadione

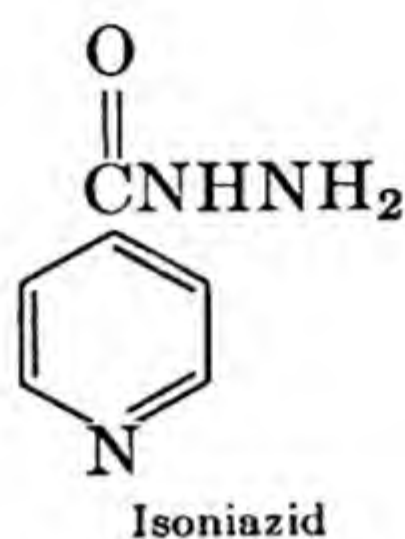


Paramethadione

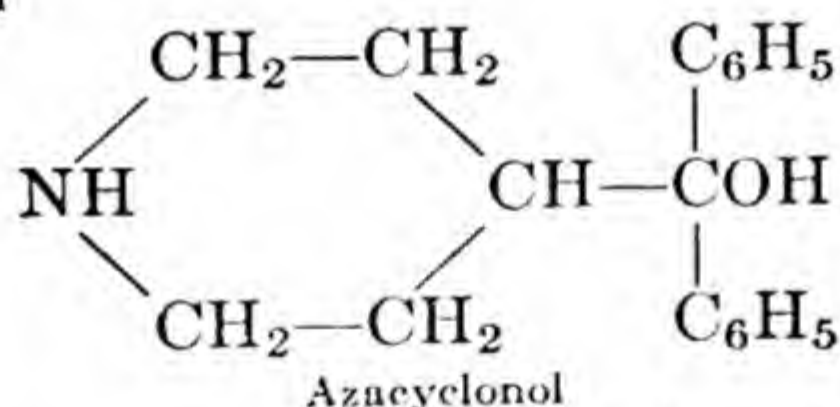
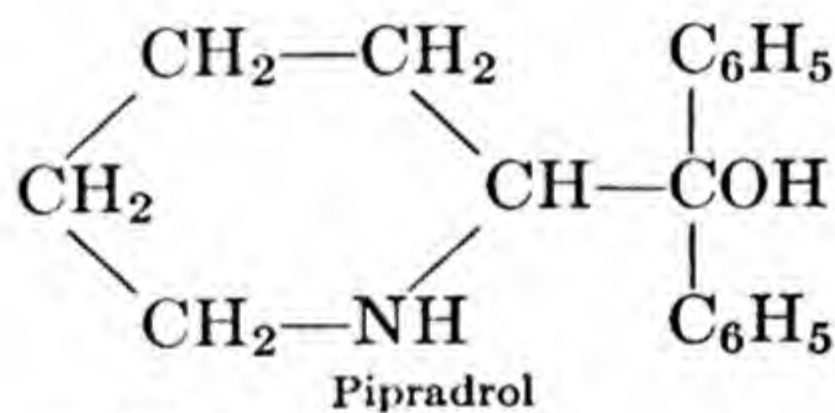
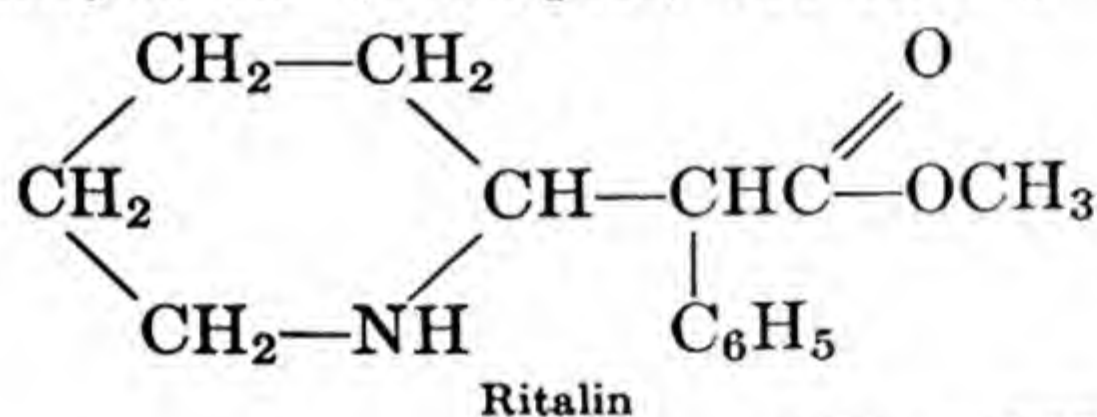
Triphenyltetrazolium chloride, a derivative of tetrazole, is employed in a test for seed viability. If the seed is alive, its embryonic tissue reduces the colorless triphenyltetrazolium salt to triphenylformazan, a red compound.



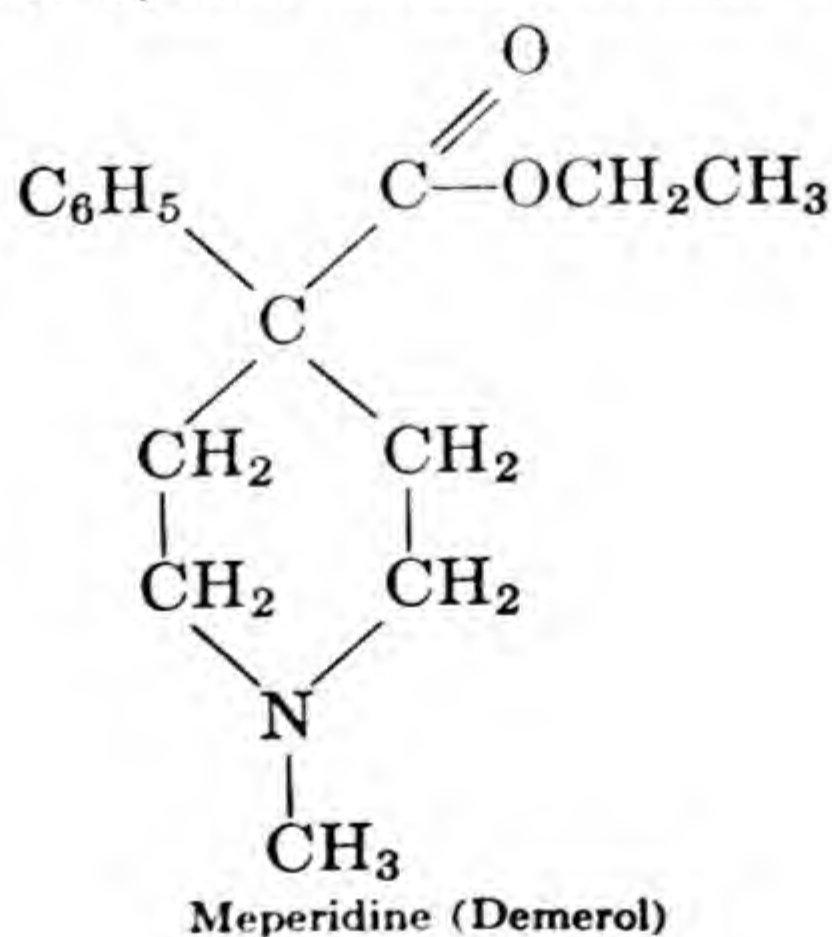
Certain pyridine derivatives have found application in medicine. Isoniazid, a derivative of isonicotinic acid, is helpful in arresting the progress of tuberculosis.



A number of piperidine (reduced pyridine) derivatives are stimulants of the central nervous system. They are also useful in relieving the depressed state and have shown promise in the treatment of some types of schizophrenia. Ritalin, pipradrol (Meratran), and azacyclonol (Frenquel) are examples:

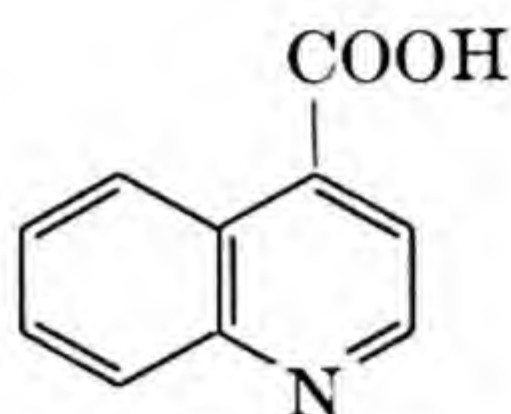


Meperidine, also a piperidine derivative, is a potent analgesic, which, like some of the opium alkaloids, can cause addiction.

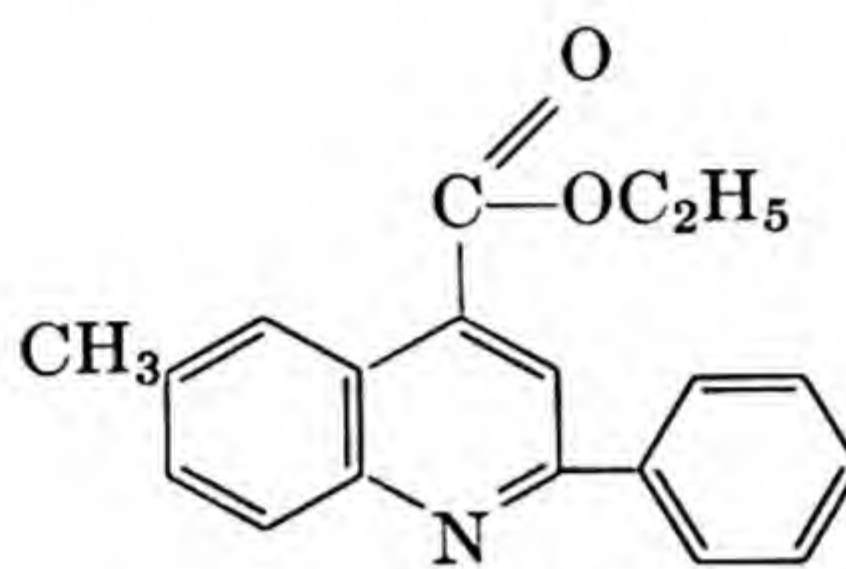




Synthetic medicinals derived from quinoline are valuable as analgesics and as antimalarials. Cinchophen and neocinchophen are more effective than most analgesics in alleviating pain in the joints and bones and are, therefore, prescribed primarily for such diseases as arthritis and gout.

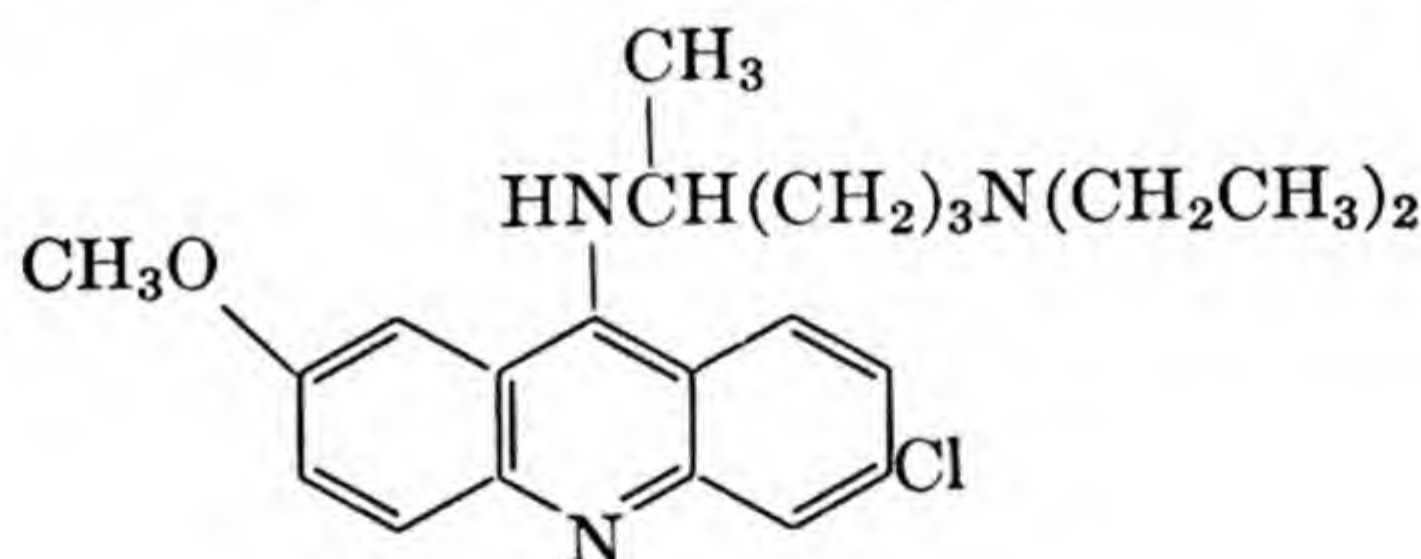


Cinchophen



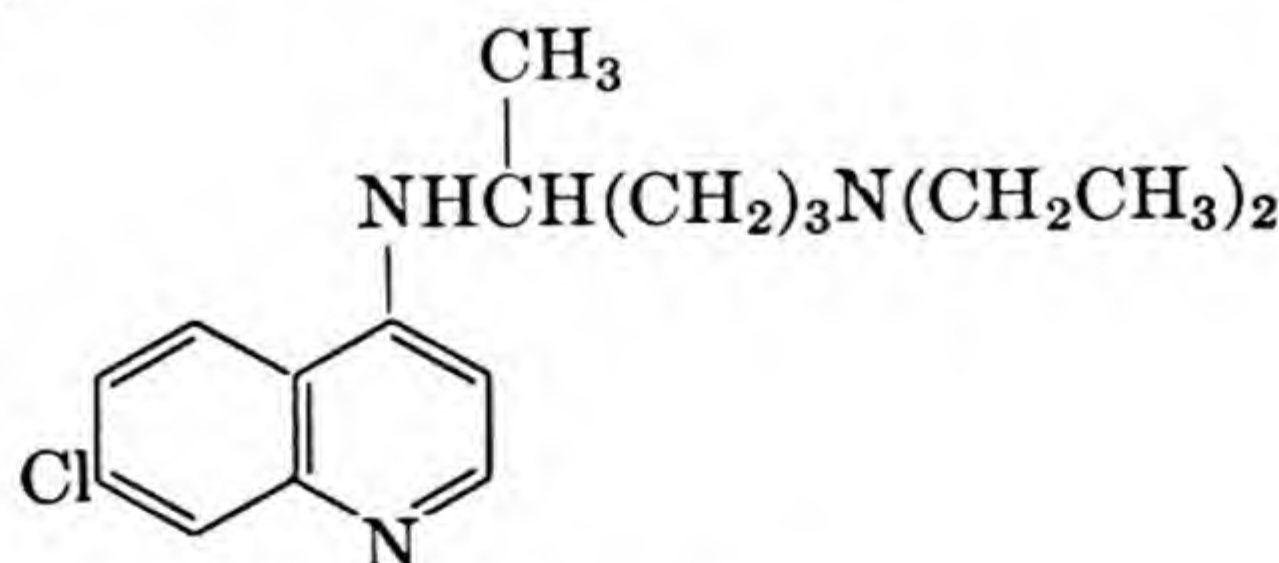
Neocinchophen

Quinine, a quinoline derivative (p. 244), obtained from the bark of the cinchona tree which grows in the East Indies, has long been known for its antimalarial properties. When the source of quinine was cut off during World War II synthetic antimalarials had to be used. The most important of these was quinacrine (Atabrine), which was consumed in tremendous amounts because of its suppressive effect. It colors the skin yellow, and therefore its use has psy-

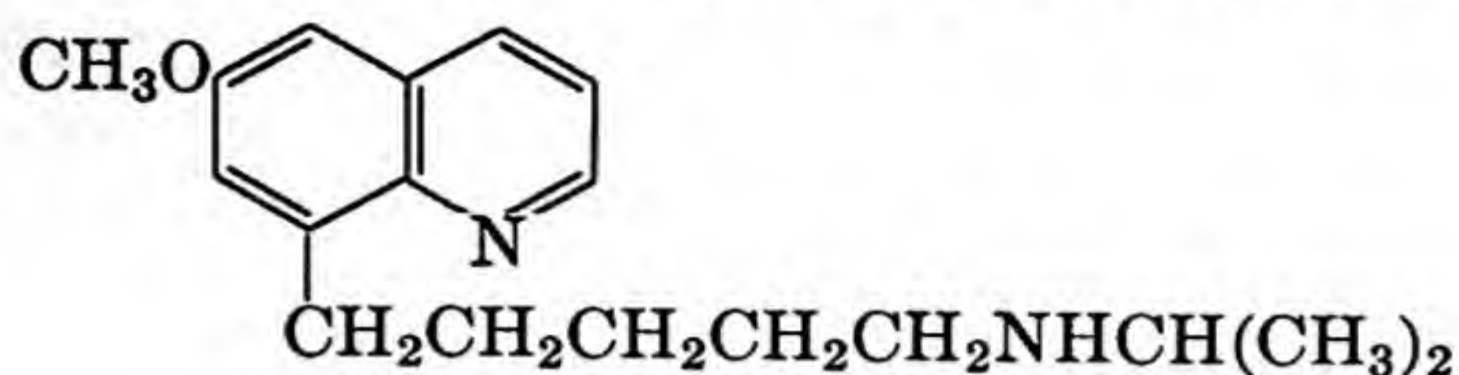


Quinacrine

chological disadvantages, though the pigmentation gradually disappears when administration of the drug is discontinued. Intensive research uncovered a number of other antimalarials with properties equal or superior to those of quinacrine. Most of these are derivatives of 4-amino- or 8-aminoquinoline. Examples are chloroquine and pentaquine:

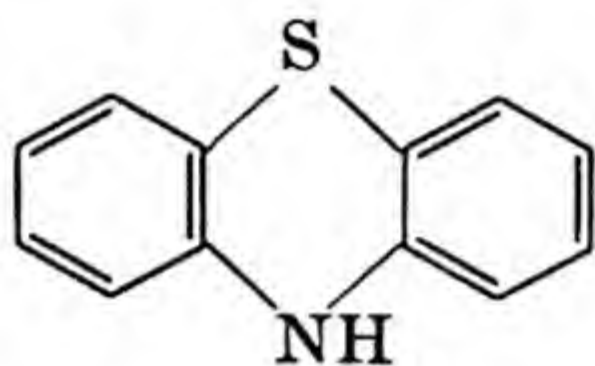


Chloroquine

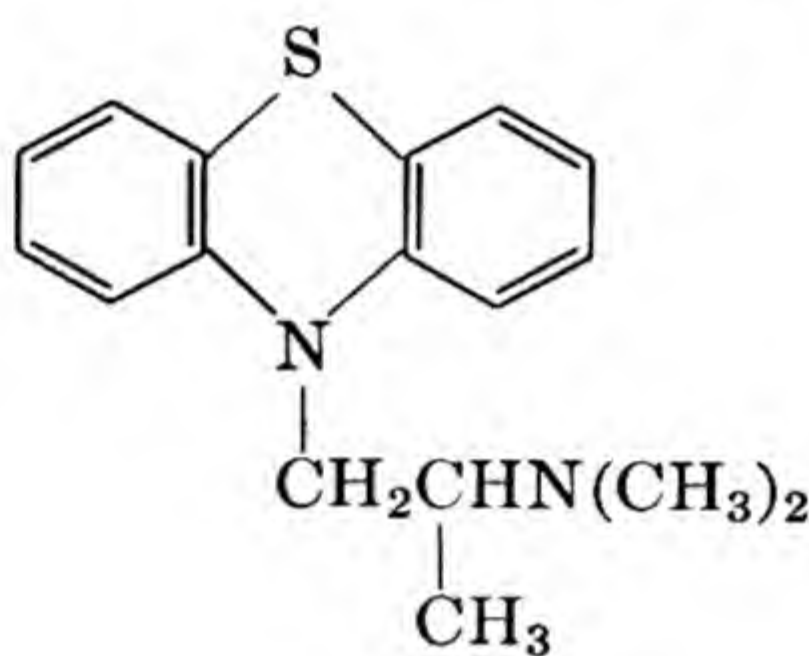


**Pentaquine**

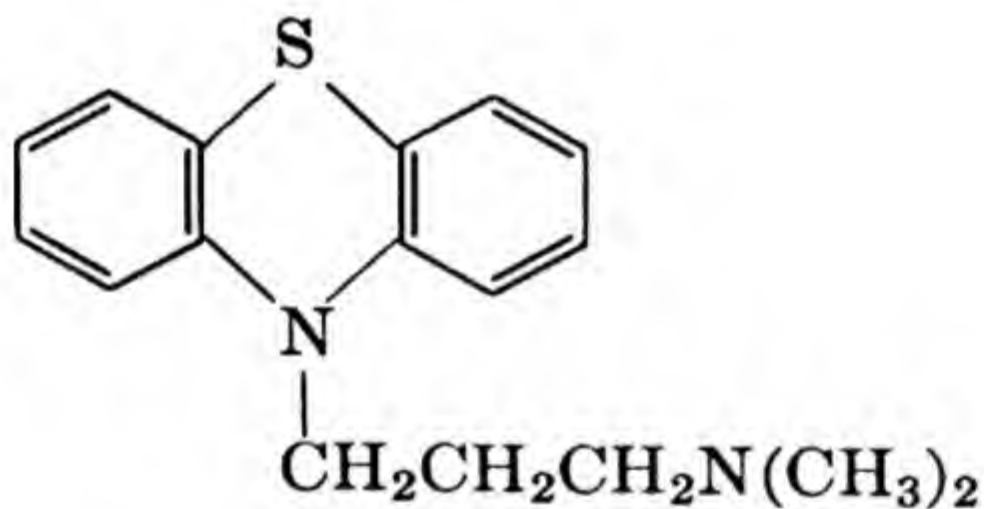
The phenothiazine ring system is a fruitful source of compounds of medicinal value. Phenothiazine itself is effective in dealing with worms in sheep and cattle. Promethazine has antihistamine properties and is structurally interesting because of its close similarity to promazine and chlorpromazine, which have tranquilizing properties.



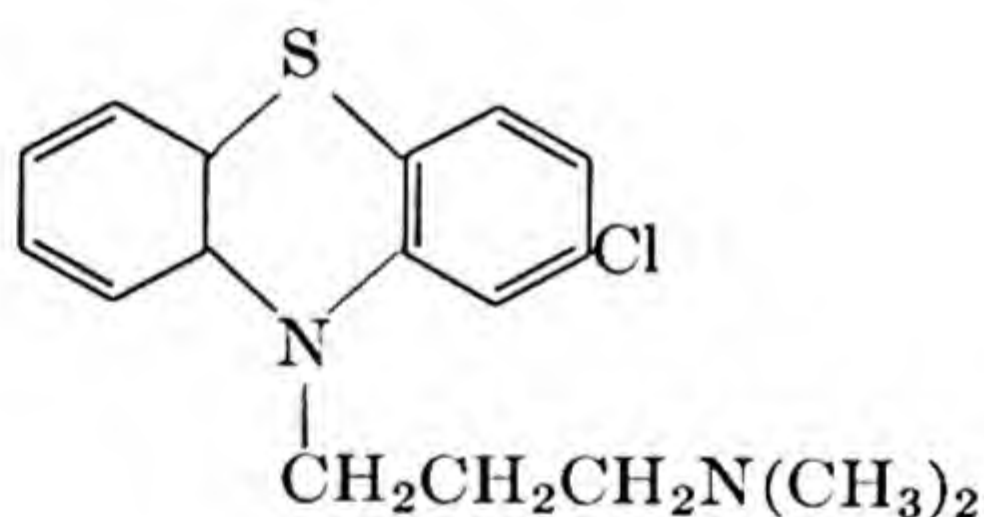
**Phenothiazine**



**Promethazine**

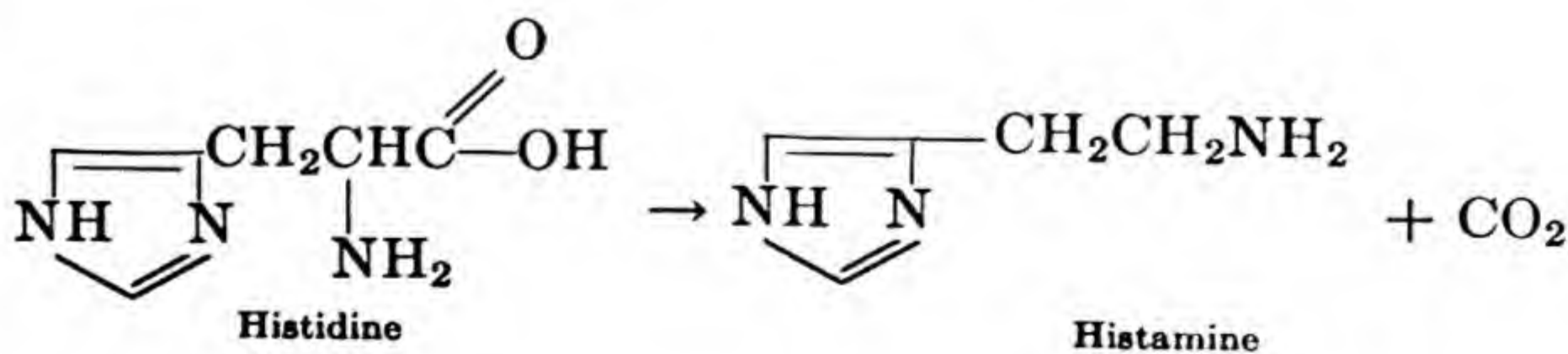


**Promazine**



**Chlorpromazine**

The antihistamines constitute a large class of medicinals which for the most part are heterocyclic substances. They are employed in the symptomatic relief of allergic manifestations. The rashes, wheals, and itching experienced in allergies are thought to be caused by histamine, which is probably formed in the body from histidine in an immunological reaction.

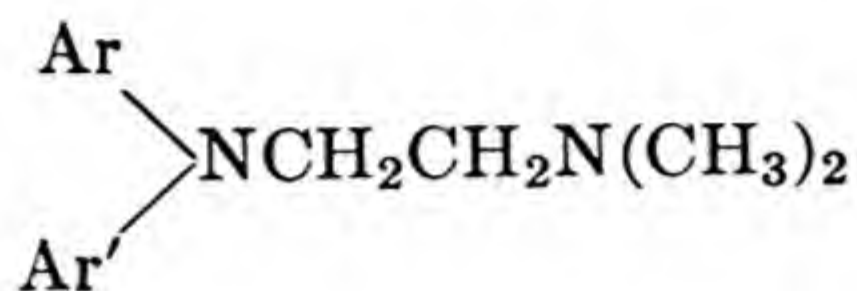


**Histidine**

**Histamine**

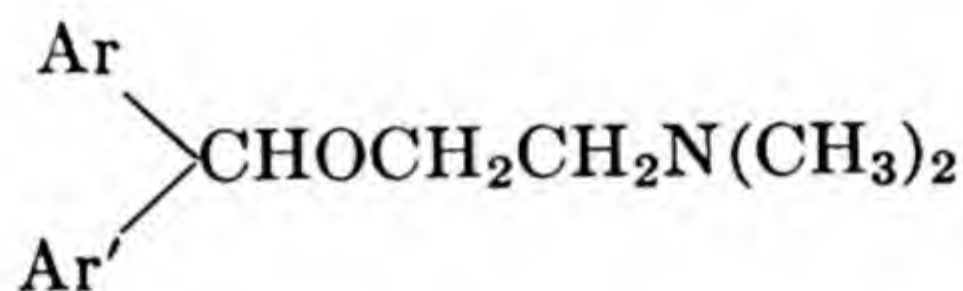


The antihistamines can be grouped into three structural classes. The ethylenediamine derivatives are not numerous; they can in most cases be related to the general formula in which the aromatic groups



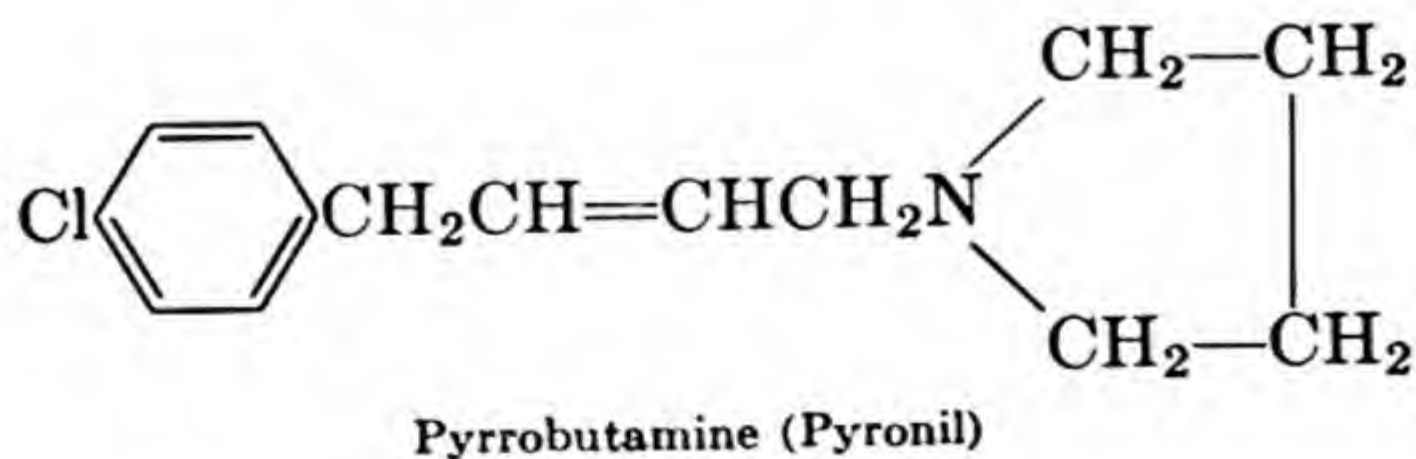
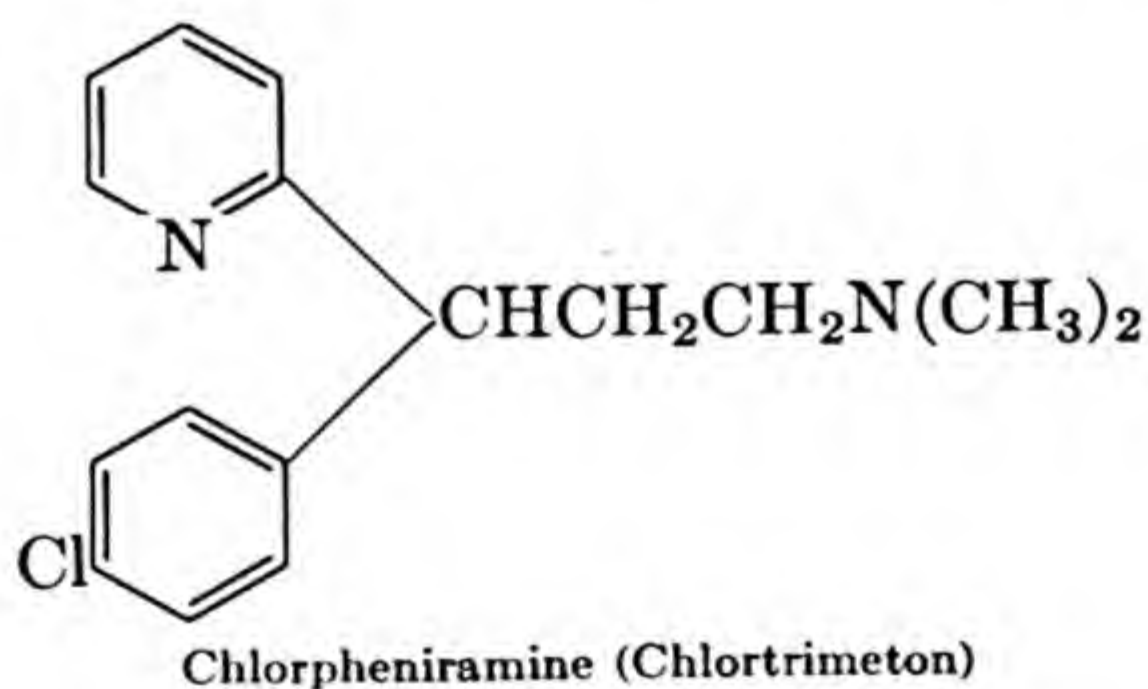
may be benzenoid or heterocyclic. Many of the common antihistamines are members of this group. Among them are methaphenilene, methafurylene, thenylpyramine (Histadyl and Thenylene), pyrila-mine, thonzylamine, thenyldiamine, antazoline, promethazine, and tripelennamine (Pyribenzamine).

A second structural type is derived from ethanolamine. It has this general formula:

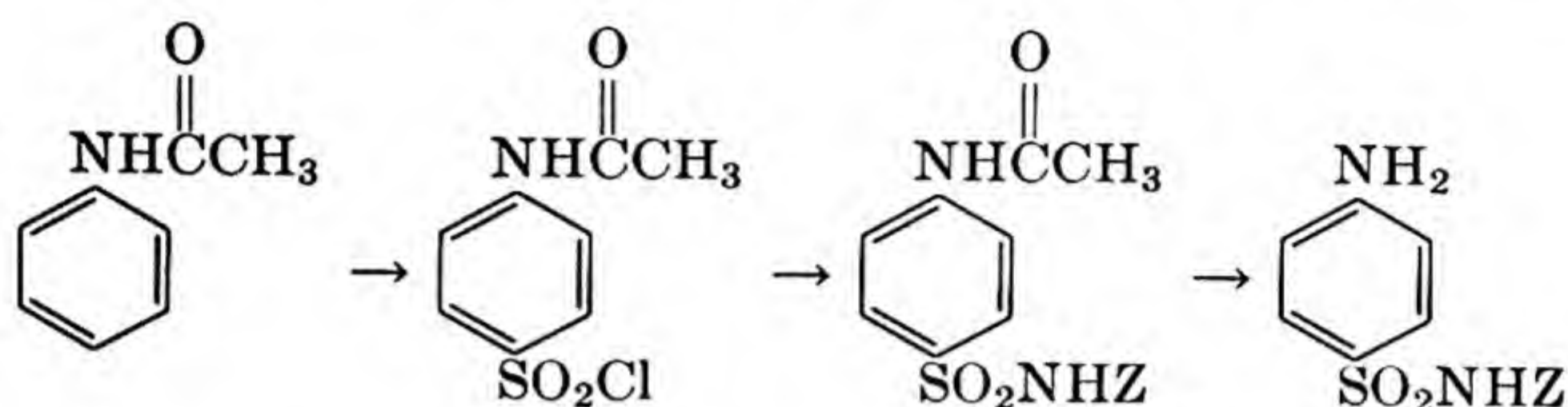


Examples are diphenhydramine (Benadryl) and paracarbinoxamine (Clistin).

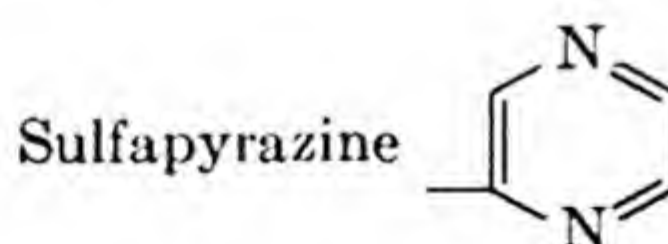
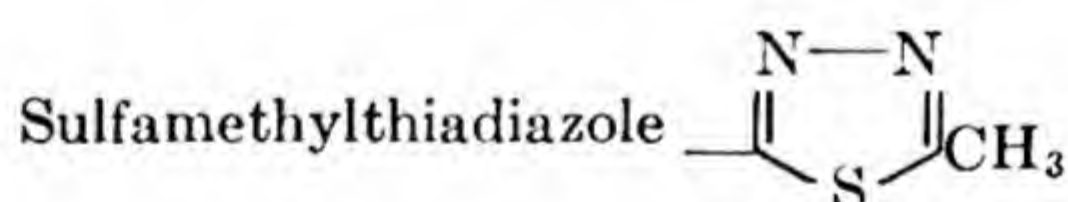
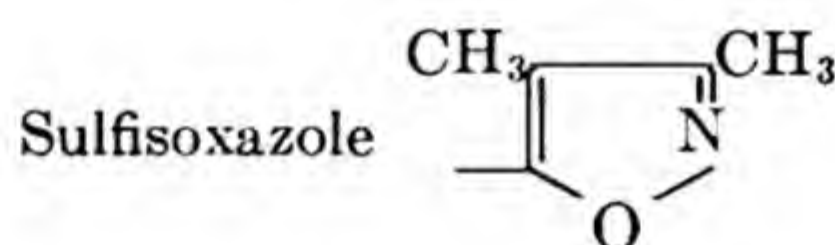
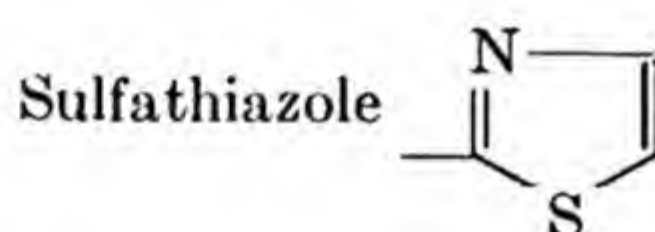
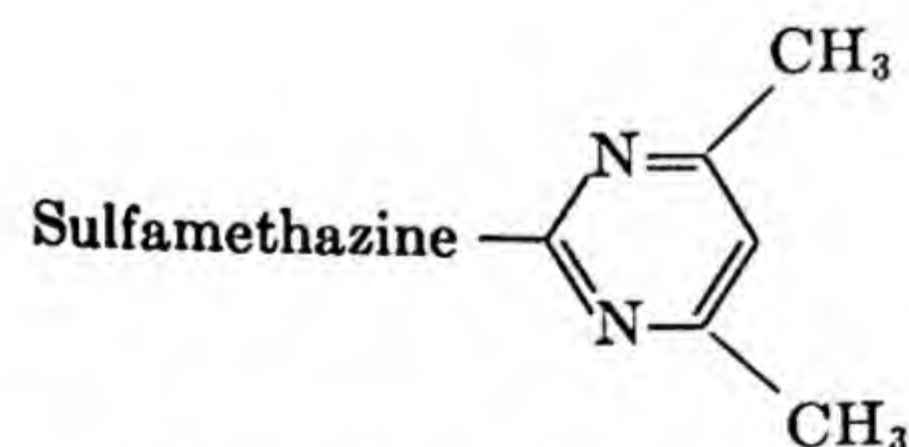
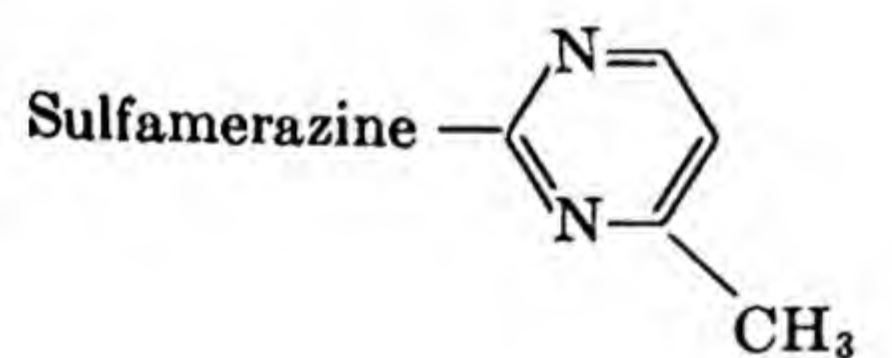
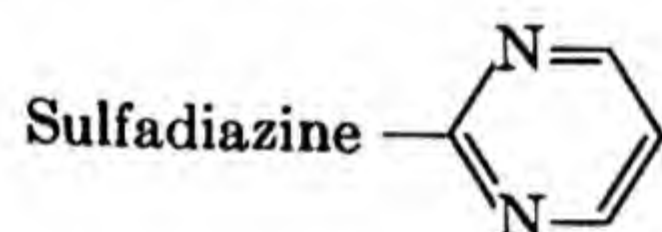
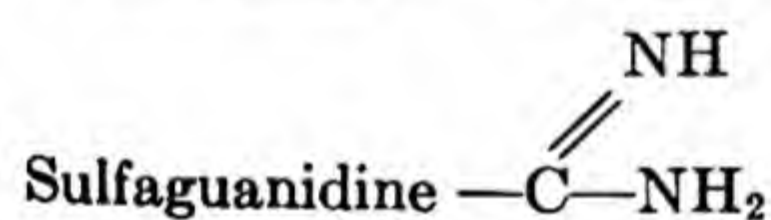
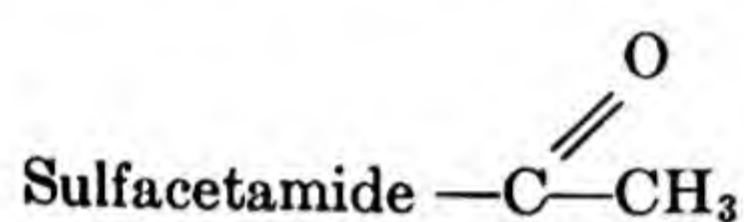
The third class is a miscellaneous one. Though its compounds are not derivatives of either ethylenediamine or ethanolamine, an inspection of the structural formulas of two examples, chlorpheniramine and pyrrobutamine, shows some structural similarities:



The sulfa drugs are another class of medicinals, most of which are heterocyclic. Over 1000 sulfa drugs have been tested, but only about fifteen or twenty are used, some only rarely. The majority of these compounds are prepared according to the sequence of reactions given below. Introduction of the chlorosulfonyl group into acetanilide is accomplished by chlorosulfonic acid,  $\text{ClSO}_3\text{H}$ . The *p*-acetaminoben-



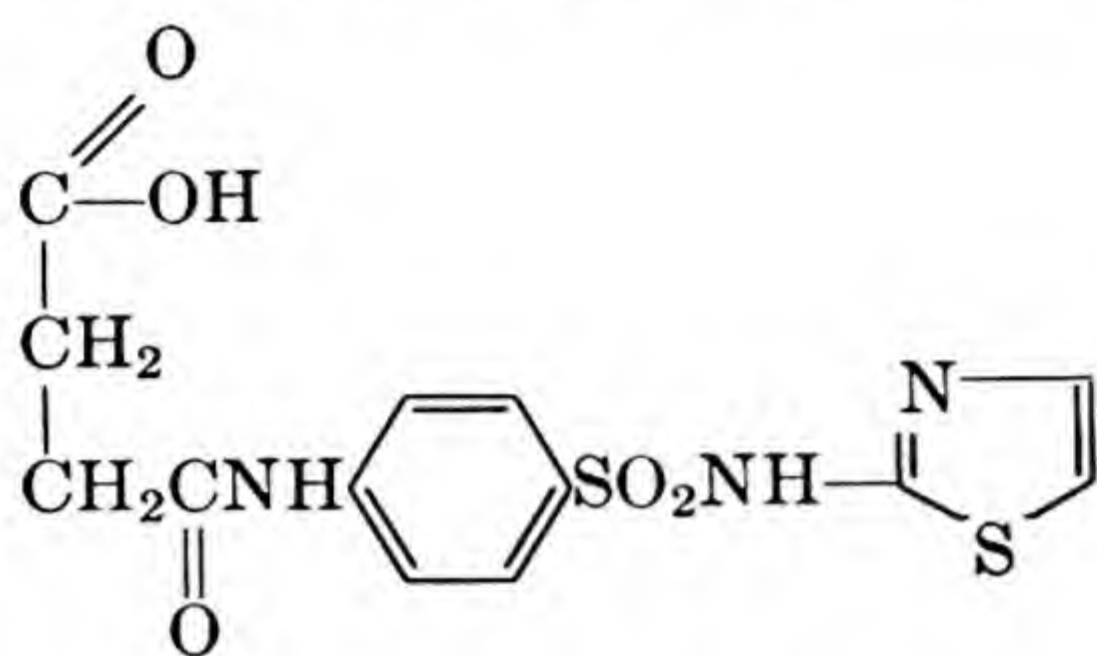
zenesulfonyl chloride is treated with the appropriate primary amine, and finally the acetyl group is removed by hydrolysis, usually in alkaline solution. In the more frequently employed sulfa drugs "Z" has the identity shown in the following table.



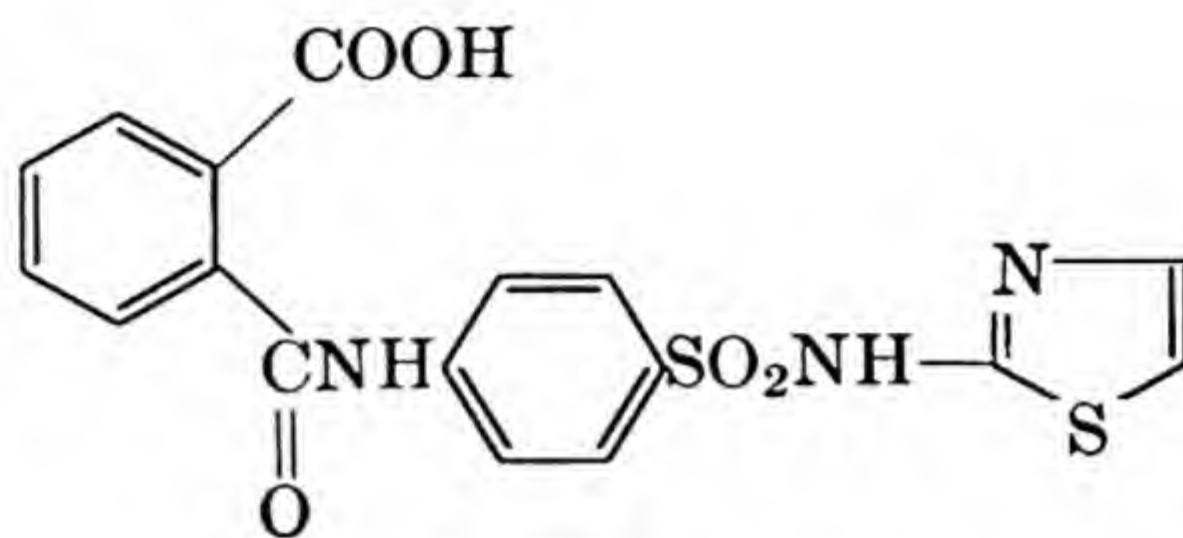
Succinylsulfathiazole and phthalylsulfathiazole are sometimes given before intestinal surgery. They are very poorly absorbed from



the intestine and are therefore effective in reducing the bacterial count of the intestinal contents.



Succinylsulfathiazole



Phthalylsulfathiazole

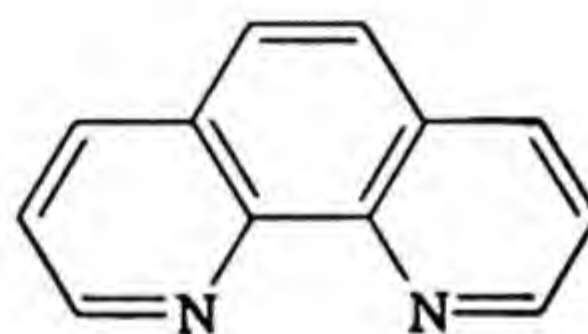
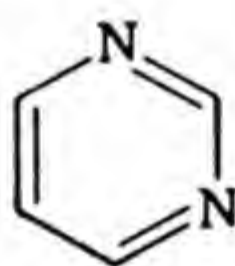
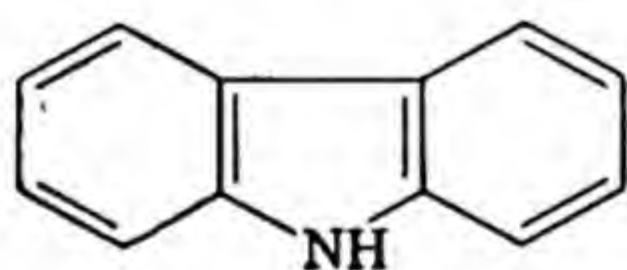
## ► QUESTIONS \_\_\_\_\_

1. Write the formulas and names for six heterocyclic compounds encountered in preceding chapters.

2. Write structural formulas for the following compounds: 2-chloroindole, 3-methylpyridine, sodium furoate, piperidine.

3. Write the formulas for and name the products produced when 1,2-dibenzoylthane ( $\text{C}_6\text{H}_5\text{COCH}_2\text{CH}_2\text{COC}_6\text{H}_5$ ) is heated with (a)  $\text{P}_2\text{O}_5$ ; (b)  $\text{P}_2\text{S}_5$ ; (c)  $\text{NH}_3$ .

4. For the following heterocyclic systems state the number of possible monosubstitution products.



# The mechanisms of organic reactions

The rupture of a covalent bond, which occurs in nearly all reactions involving organic compounds, can take place in two distinctly different ways. In Equation 1 the two electrons forming the covalent bond are separated, and each portion retains one of them. The fragments  $X\cdot$  and  $Y\cdot$  thus produced are electrically neutral.



Either X or Y may be composed of a single atom, such as  $:\ddot{\text{Cl}}\cdot$ , or a

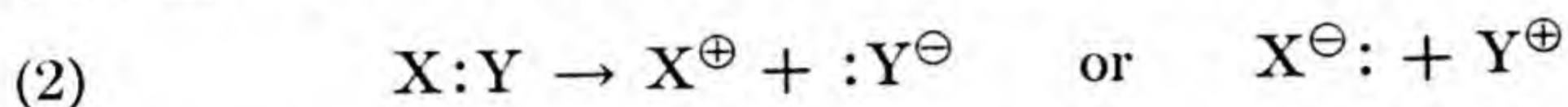
group of atoms, such as methyl,  $\text{H}:\ddot{\text{C}}\cdot$ . An electrically neutral combination of atoms having a single unpaired electron is called a *radical*;

thus  $\text{H}:\ddot{\text{C}}\cdot$  is the *methyl radical*. Reactions which occur by a cleavage



of a covalent bond to give radicals are said to proceed by a radical mechanism.

In Equation 2 the cleavage has occurred so that one atom possesses both of the bonding electrons. If the two components of the original molecule  $XY$  are different, either portion might acquire both electrons.



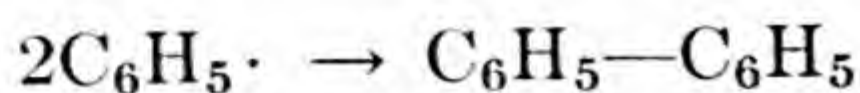
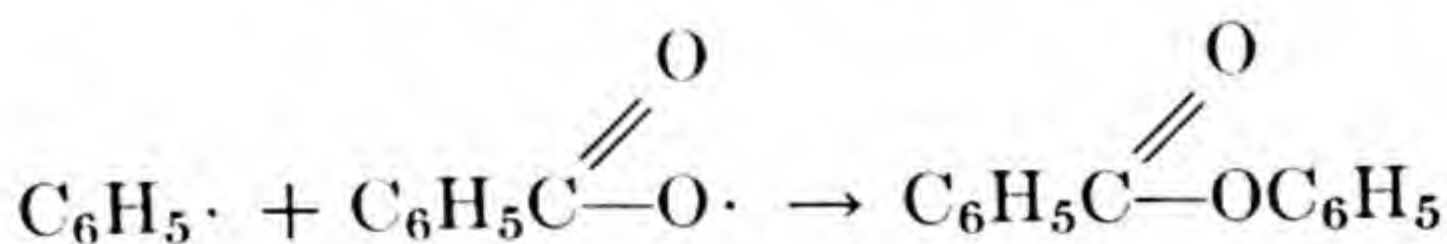
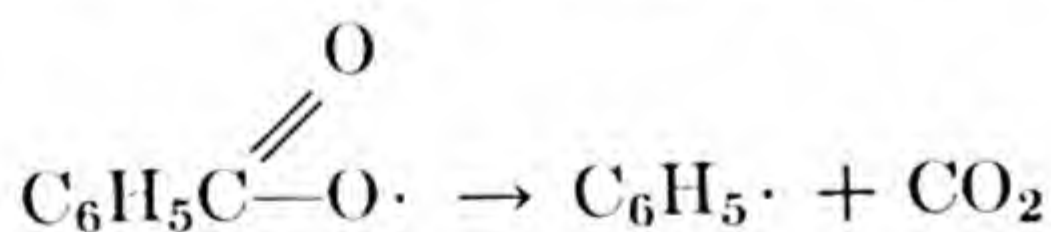
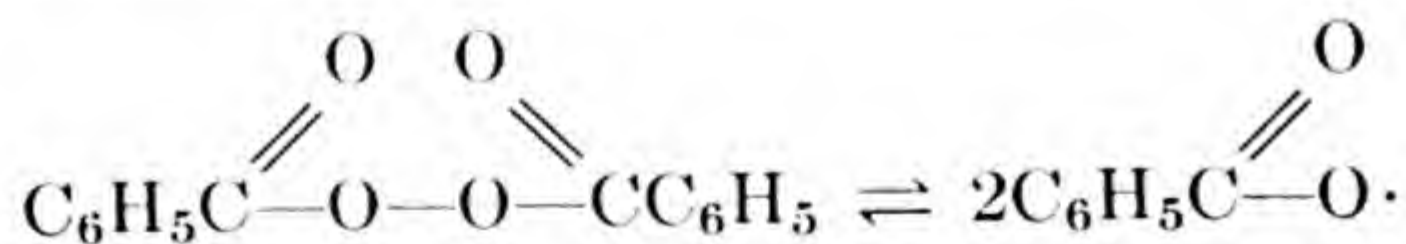
In principle, the two alternatives are the same; the fragments are electrically charged, since one is deficient by one electron and the other has an extra electron. Because the fragments are ions a reaction in which the type of rupture represented by Equation 2 occurs is said to proceed by an ionic mechanism.

The characteristics of the two types of reaction are quite different. Nearly all gas phase reactions are the radical type. When they occur in solution radical reactions are usually not profoundly affected by the solvent. Ionic reactions, on the other hand, are appreciably influenced. Radical reactions are usually initiated by radiation or by other free radicals, whereas most ionic reactions are catalyzed by acids, bases, or other ionic compounds. Radical reactions frequently exhibit induction periods, and many of them are the chain type.

It should be noted that many of the radicals and ions proposed as intermediates in reactions are very short lived. In numerous instances the evidence of their existence is circumstantial.

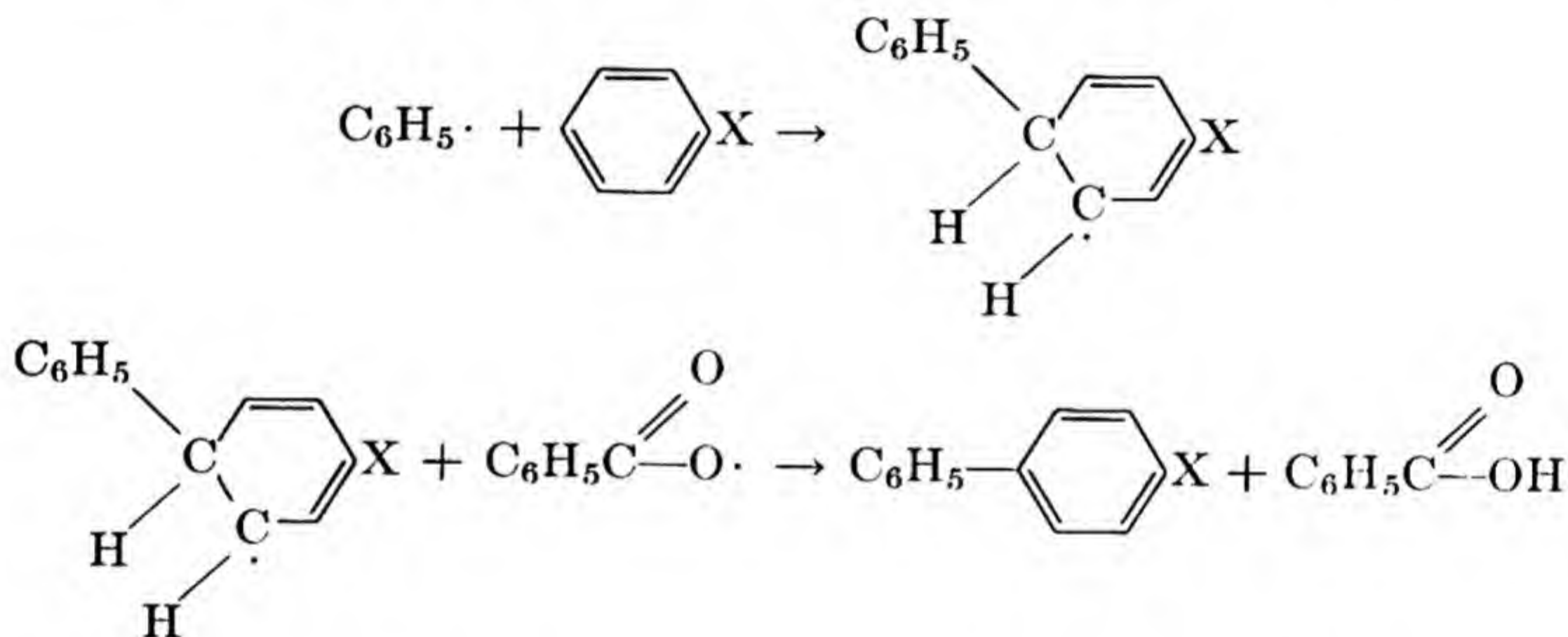
## ► RADICAL REACTIONS

**Thermal Decomposition.** It is likely that thermal decompositions in general occur by radical mechanisms. A reaction of this type which has been studied is the decomposition of benzoyl peroxide; the following reactions occur:

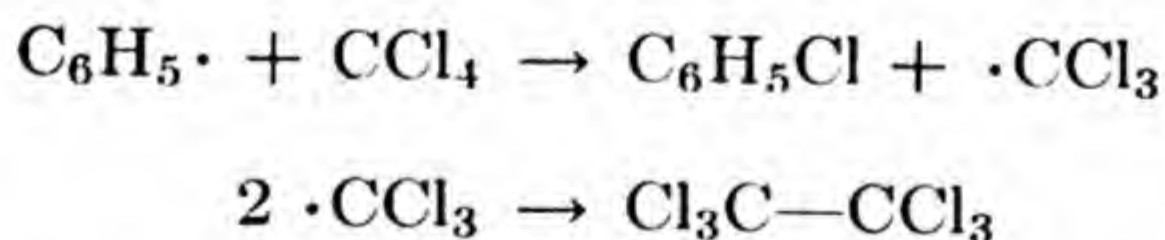




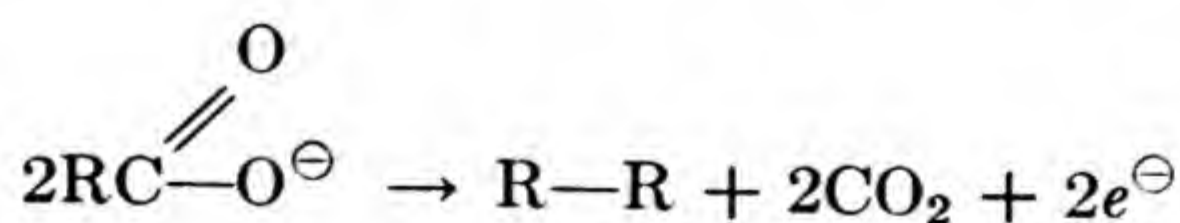
For clarity, the formulas for the radicals are shown in a somewhat abbreviated form. Each of the radicals depicted here has an atom with seven electrons in its outer shell; the other atoms have two or eight (complete outer shells). In the first reaction scission of the O—O bond occurs, and each oxygen atom then has seven electrons. The benzoate radicals thus produced can undergo further decomposition to give phenyl radicals and carbon dioxide. The phenyl radicals can combine with each other or with the benzoate radical, as in the last two equations, or can react with the solvent if one is present. If the solvent is a substituted benzene, it reacts primarily at the *para* position. The new radical may stabilize itself by reaction with another radical. The same *para* substitution occurs whether the group X orients *ortho-para* or *meta*, and thus radical substitution of benzene derivatives does not obey the usual orientation rules.



If the decomposition of benzoyl peroxide is performed in carbon tetrachloride, the phenyl radical abstracts a chlorine atom from the solvent.



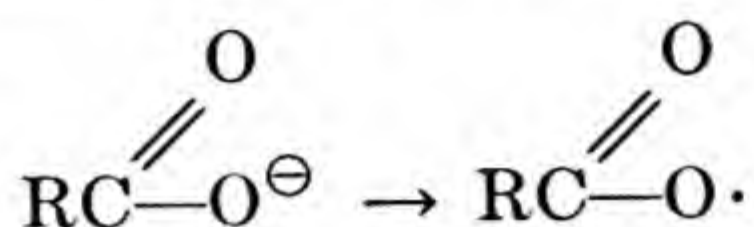
**Kolbe Electrolysis.** When an electric current is passed through a water solution of a soluble salt of a carboxylic acid a hydrocarbon results.



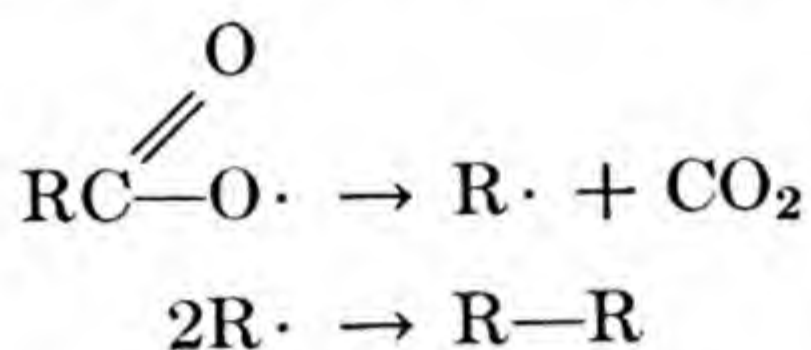
It is likely that the first step in the reaction is the discharge of the



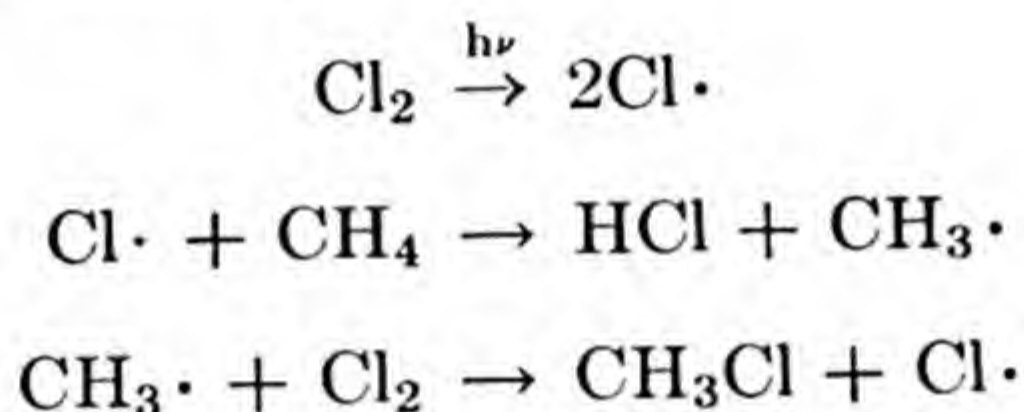
carboxylate ion at the anode; this yields a radical. The radical then



loses carbon dioxide (as with the benzoate radical previously mentioned), and finally two  $\text{R}^\bullet$  radicals unite to give the hydrocarbon.

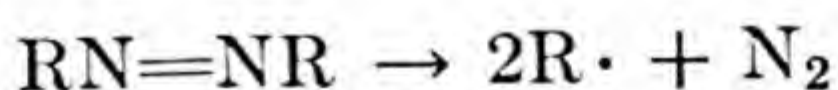


**Halogenation of Paraffins.** The reaction of elemental chlorine with methane is in many ways a typical radical reaction. The following steps illustrate the process:

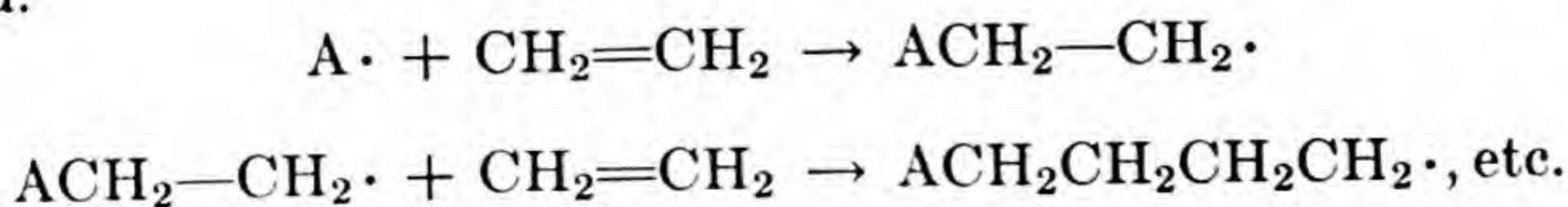


The chlorine molecule is converted by radiation (ultraviolet) into chlorine atoms (radicals) which react with methane to give hydrogen chloride and methyl radicals. A methyl radical attacks another chlorine molecule and produces methyl chloride and a chlorine atom. Thus the reaction is theoretically self-sustaining—a chain reaction. Chain reactions are stopped when the radicals react with each other or with solvents.

**Polymerization.** Numerous polymerization reactions are known in which initiation is accomplished by a radical generator. Peroxides, in general, serve the purpose, and aliphatic or alicyclic azo compounds are also used. They evolve nitrogen and produce radicals when heated.



The polymerization of ethylene is depicted as follows, where  $\text{A}^\bullet$  is the radical. The reaction stops in any of the ways previously mentioned.





## ► IONIC REACTIONS

Many of the reactions of the ionic type can be considered as extensions of simple acid-base reactions. The reacting molecules must be so constituted that an electron deficiency in one (the acid) may be satisfied by a pair of electrons from the other (the base). In fact, many reactions which proceed *via* an ionic mechanism are catalyzed by acids.

**The Addition of Halogen to Olefins.** Because of the usual method of representation we are inclined to think of the double bond as the equivalent of two single bonds. However, the two bonds making up the double bond differ from each other. One of them, the

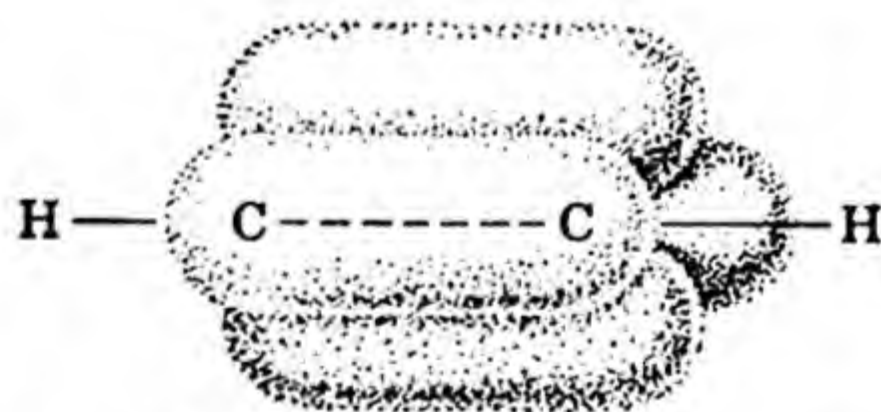
The  $\pi$  bond in ethylene is best represented by a volume above and below the plane of the carbon and hydrogen nuclei. The  $\sigma$  bond is not shown in the drawing.



*The  $\pi$  Bond in Ethylene*

$\sigma$  (sigma) bond, is very much like a single bond, but the other, the  $\pi$  (pi) bond, has different properties. It is the  $\pi$  bond which undergoes the addition reactions characteristic of olefins. The electrons composing the  $\pi$  bond may be said to be located in an area surrounding the  $\sigma$  bond, and thus we may think of a double bond as having a

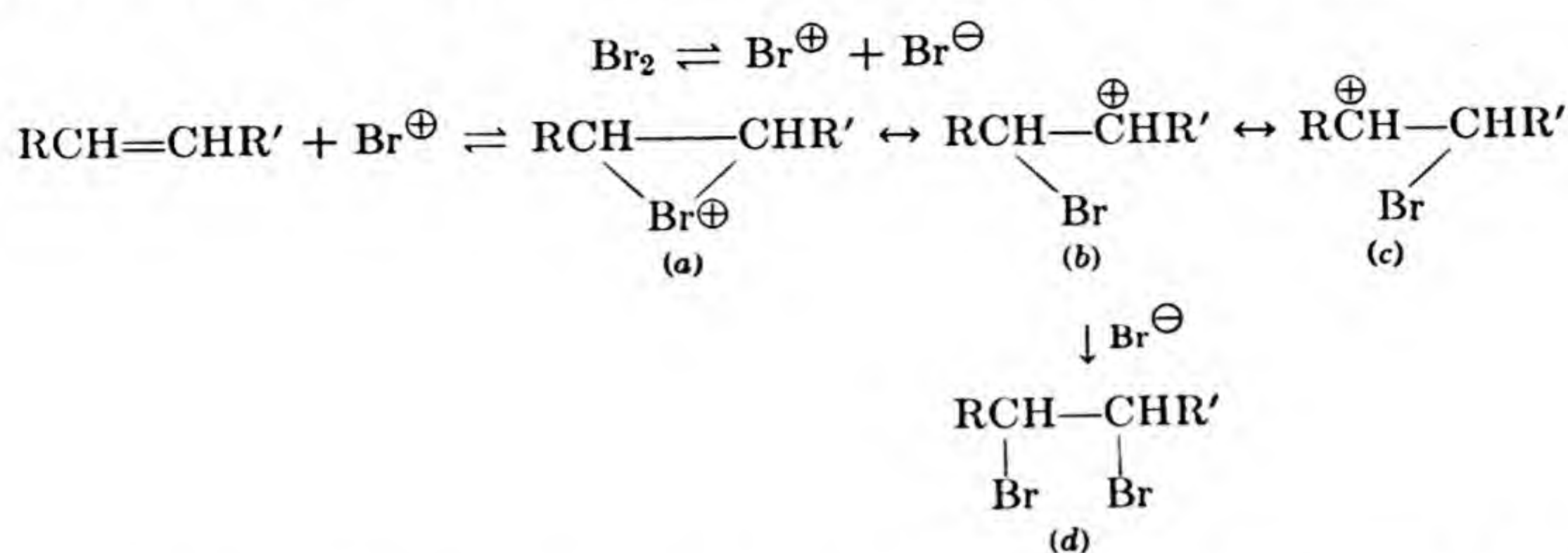
The two  $\pi$  bonds in acetylene are represented by the same type of diagram as for ethylene. The volumes represented by the two bonds are situated at right angles to each other.



*The Two  $\pi$  Bonds in Acetylene*

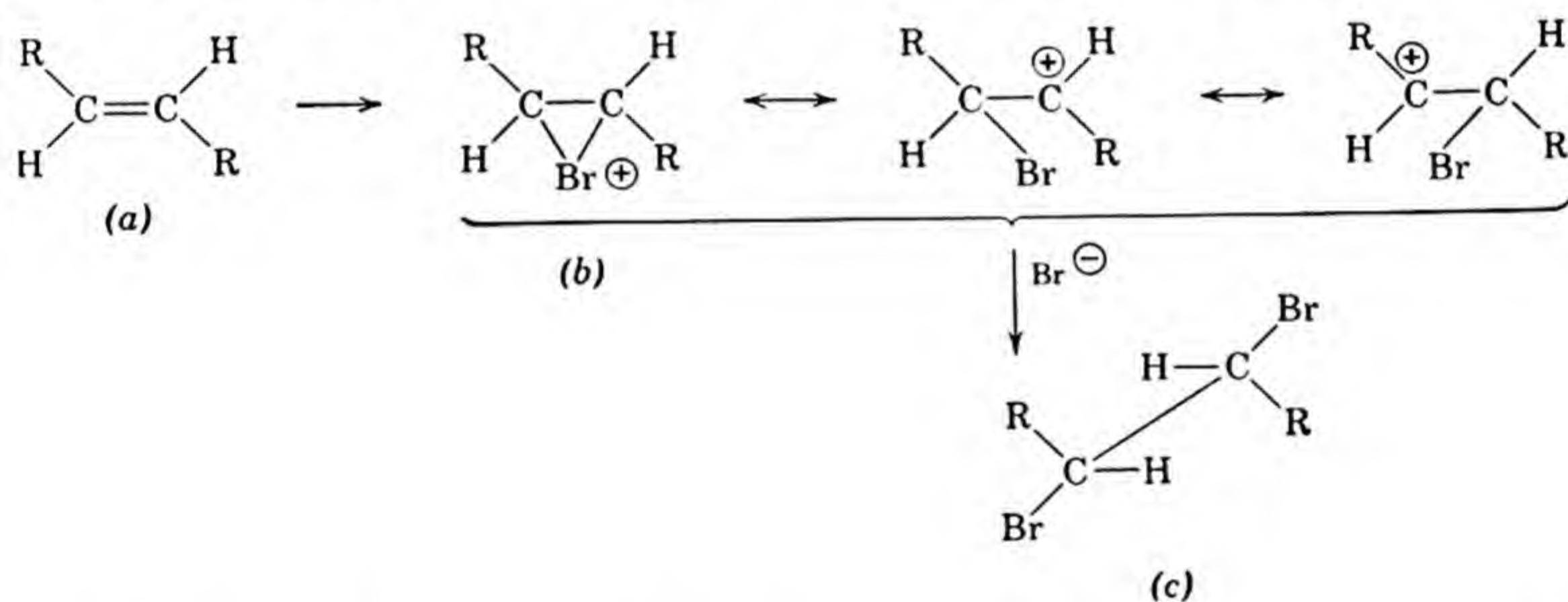
negative charge surrounding it. It will therefore attract positively charged ions. Bromine shows a slight tendency to ionize into a positive and a negative ion. This tendency can be enhanced by the use of catalysts. When the positive bromine ion adds to the double bond a positively charged ion is produced which may be considered a hybrid of the resonance structures *a*, *b*, and *c*. This ion, of course,





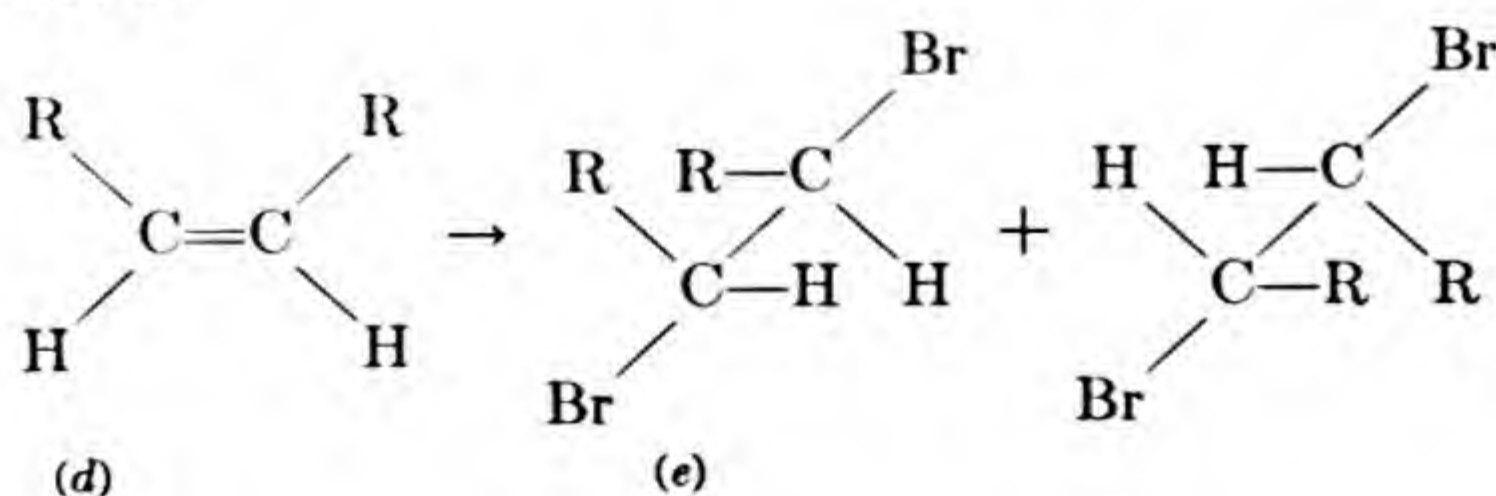
attracts the bromide ion to yield the familiar dibromo product *d*. The bromonium ion (*a*, *b*, *c*) is postulated as a resonance hybrid because of the stereochemistry of the reaction.

Different optical isomers are obtained when the *cis*- and *trans*-isomers are treated separately with bromine. The approach of the positive bromine ion would be expected to occur from either above or below the double bond as in the illustration. The bulk of the

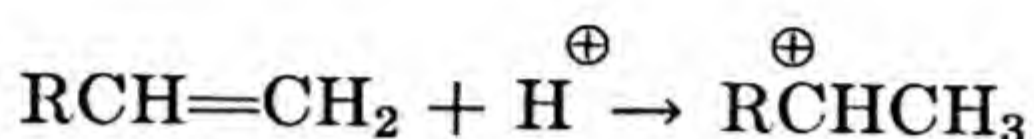


bromine atom would favor the approach of the negative bromide from the opposite side, so that *c* would be the expected product. The two carbon atoms have now become asymmetric, but the compound *c* is a *meso* compound because it possesses a plane of symmetry which can be easily observed by rotation of one carbon with respect to the other.

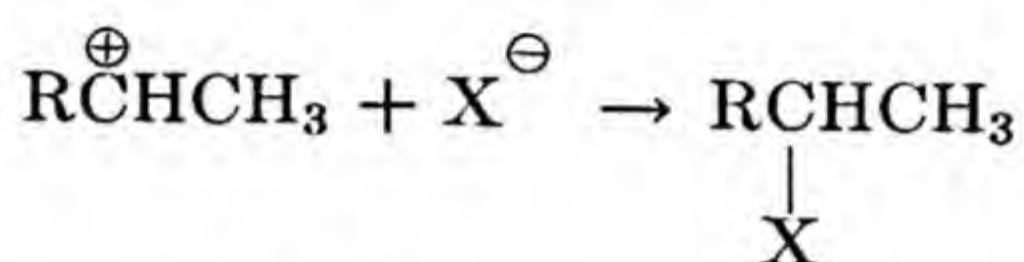
If the starting olefin were the *cis*-compound *d*, the product would be a DL mixture *e*.



**Addition of HX to Olefins.** The addition of acids, such as HX and  $\text{HOSO}_2\text{OH}$ , to olefins occurs in a fashion much like that described for elemental bromine. In the first stage the proton (from the acid) reacts with the olefin to give a positively charged ion. Such ions are said to be carbonium ions, since the carbon atom is positively



charged. The second stage is the addition of the negatively charged ion. With an unsymmetrical olefin, such as that illustrated, two



products are conceivable in an addition reaction. The second would result by addition of the proton to the other carbon atom, so that its structure would be  $\text{RCH}_2\text{CH}_2\text{X}$ . However, this product is not formed (Markovnikoff's rule). The explanation lies in the electronic behavior of the reactants. The proton is attracted more strongly by whichever carbon atom of the double bond has the higher concentration of electrons. The addition takes place as though it involved the more stable of the two possible carbonium ions. The stability of such ions is increased by contribution of electrons from adjacent C—H bonds. The ion  $\text{RCH}^{\oplus}\text{CH}_3$  has more of such bonds than  $\text{RCH}_2\text{CH}_2^{\oplus}$ .

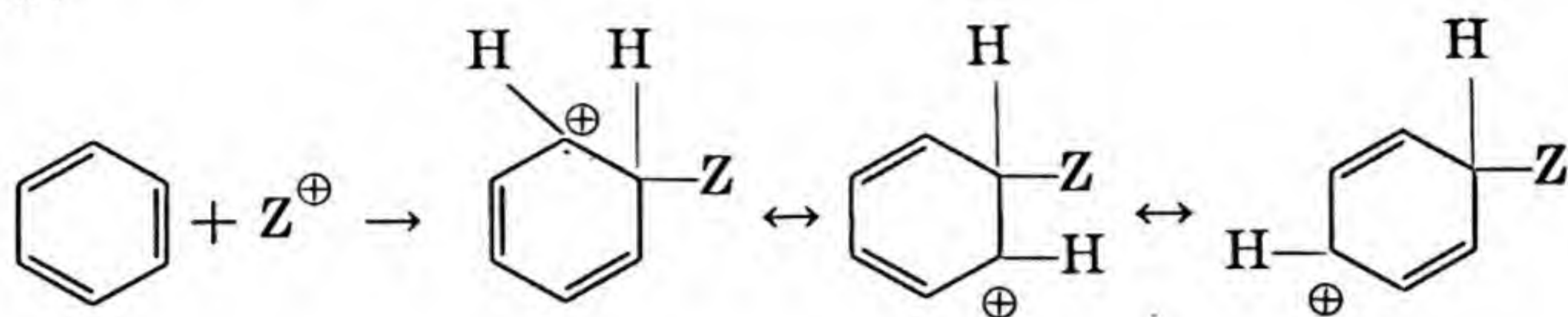
**Aromatic Substitution.** Aromatic substitution of the usual type bears certain resemblances to the addition of HX to an olefin. Electronically, benzene may be thought of as a six-membered ring in which the carbon atoms are united by single covalent bonds. The additional six electrons are the property of the whole molecule. They are most likely to be found in two regions of doughnut-shaped appear-



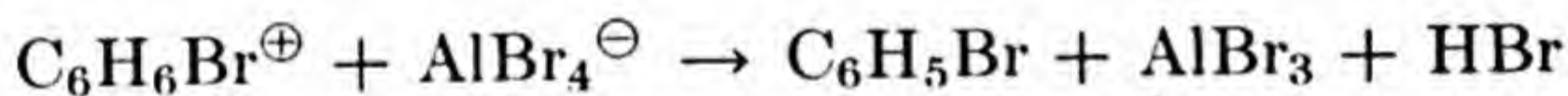
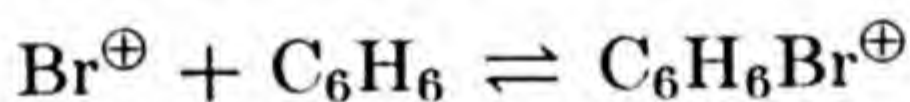
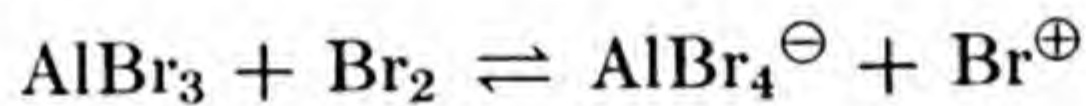
ance above and below the plane of the benzene ring. A positive ion which approaches the benzene ring is therefore strongly attracted by these electrons. This attraction is magnified considerably because of the mobility of these electrons (the inductive effect).



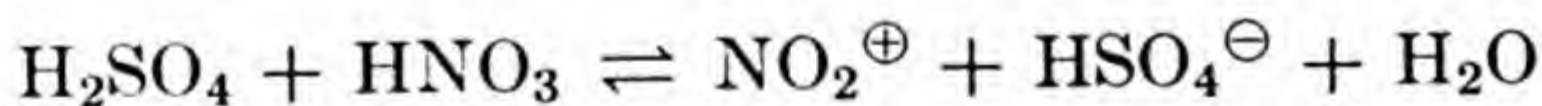
The first step in aromatic substitution can be represented as shown below.



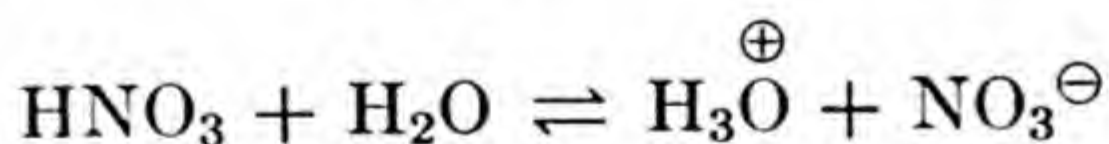
The product, which is a carbonium ion, is most conveniently represented as a resonance hybrid. The ion can stabilize itself by the expulsion of a positive ion, either that originally attacking or a proton. In the first instance benzene would be reformed; in the second a substitution product would result. It is obvious that any substance which aids in the formation of the cation  $Z^{\oplus}$  would promote aromatic substitution. Such is the function of the "carriers" used in aromatic substitution. Thus in bromination aluminum bromide seems to function as shown in the equations below. It seems unlikely, however, that the  $Br^{\oplus}$  is ever entirely free; it is so written only for simplicity.



In aromatic nitration, concentrated sulfuric acid is often used. High concentrations of this acid make the nitrating agent more efficient. It appears that sulfuric acid promotes the ionization of nitric acid to yield the nitronium ion  $NO_2^{\oplus}$ , which is the attacking species.

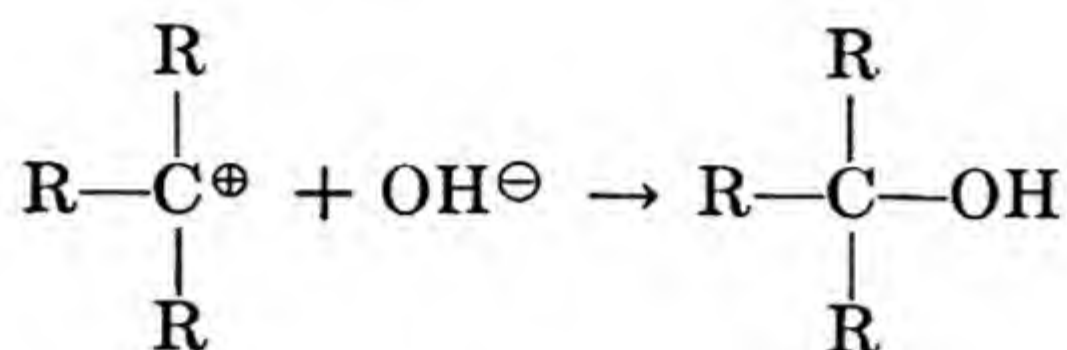
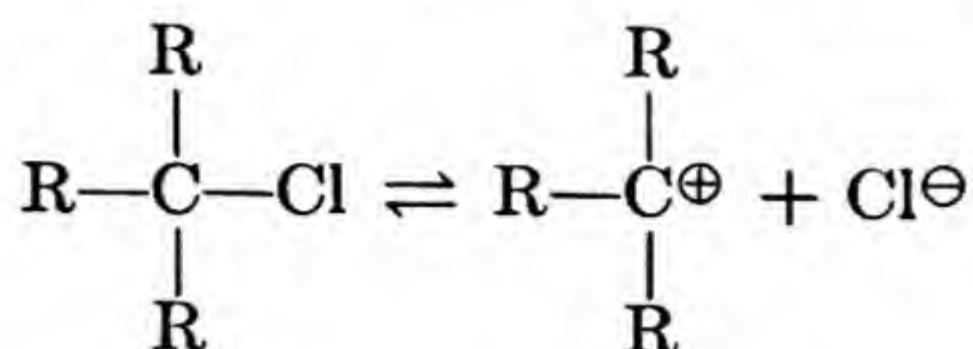


If much water is present in the nitrating mixture, the usual ionization of nitric acid occurs, and nitration is prevented.

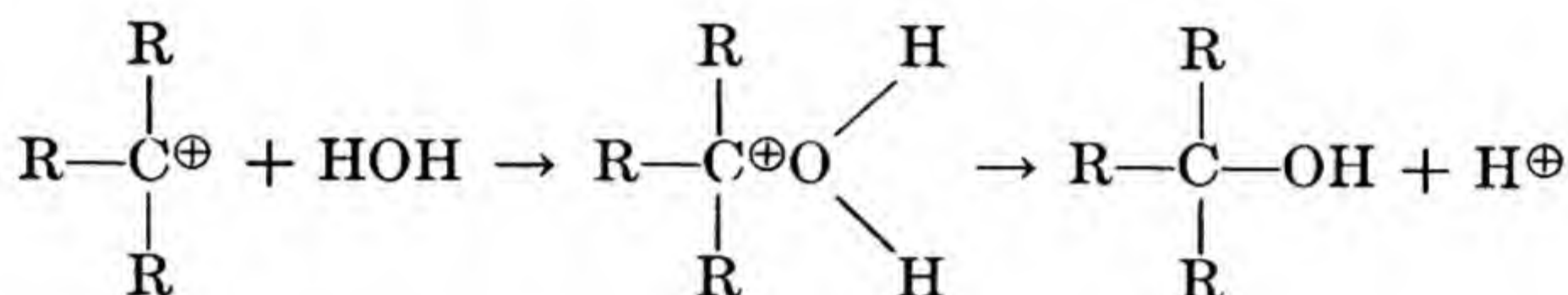


**Displacement Reactions.** A displacement reaction is one which takes the form of  $A + RB \rightleftharpoons RA + B$ . A and B may be ions or radicals, but most commonly they are ions. Displacement reactions have been more extensively studied than other types. The hydrolysis of the alkyl halides is an example. Two different mechanisms may apply, depending upon the type of halide. With tertiary and certain secondary halides, a preliminary ionization occurs.



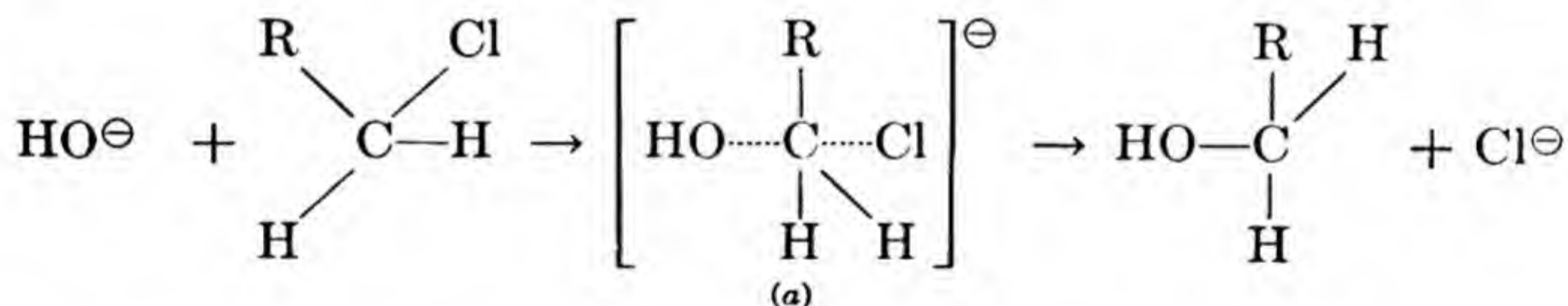


or



Though not often shown in equations of this type, solvent molecules play an important part in the reaction. In solution all ions are doubtless solvated.

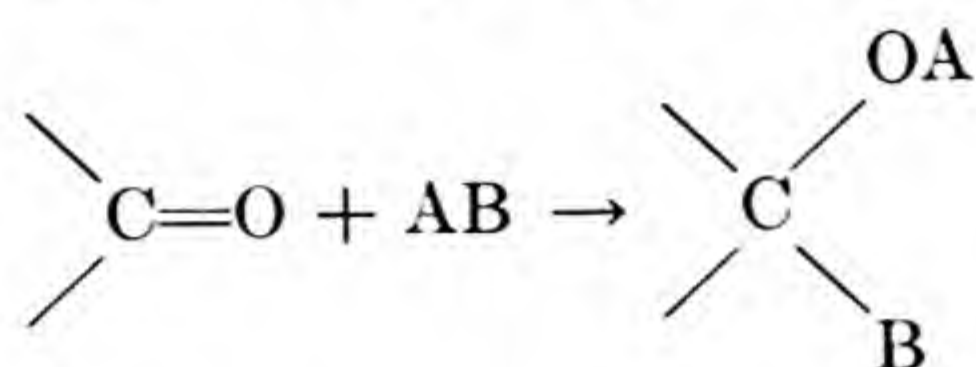
With most secondary halides and, by extension, primary halides, a different mechanism comes into play. The chief characteristic is an attack by the hydroxide ion upon the chloride molecule. Because of stereochemical considerations it is concluded that the attack occurs at the side of the molecule that is directly opposite the chlorine atom.



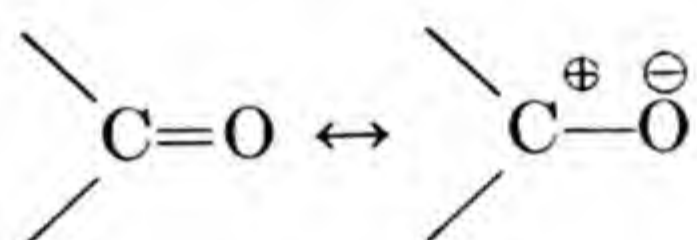
The unstable combination pictured as *a* is known as a transition state. The two hydrogen atoms, the R group, and the central carbon atom lie in one plane. The hydroxyl group and chlorine atom are situated on a line perpendicular to this plane and are visualized as bound to the carbon atom. The transition state is transitory. It is to be noted that the configuration of the carbon atom is inverted in this displacement. Investigations of numerous other displacement reactions have shown that inversion is of very common occurrence.

**Additions to Aldehydes and Ketones.** A great number of reactions are known which involve addition to the carbonyl group. In most such reactions A is hydrogen; an outstanding exception is the

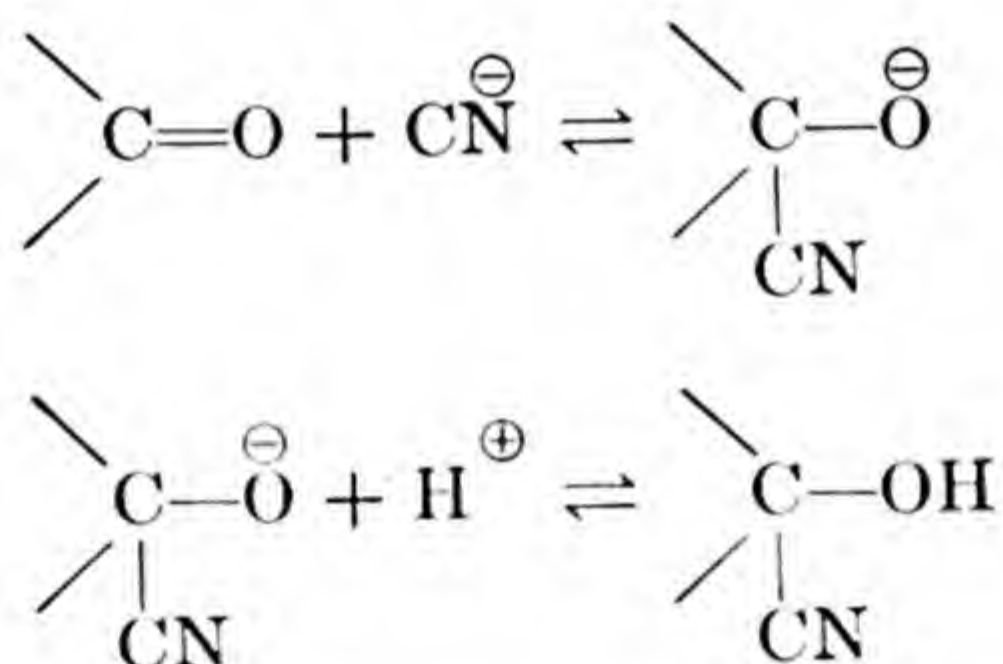




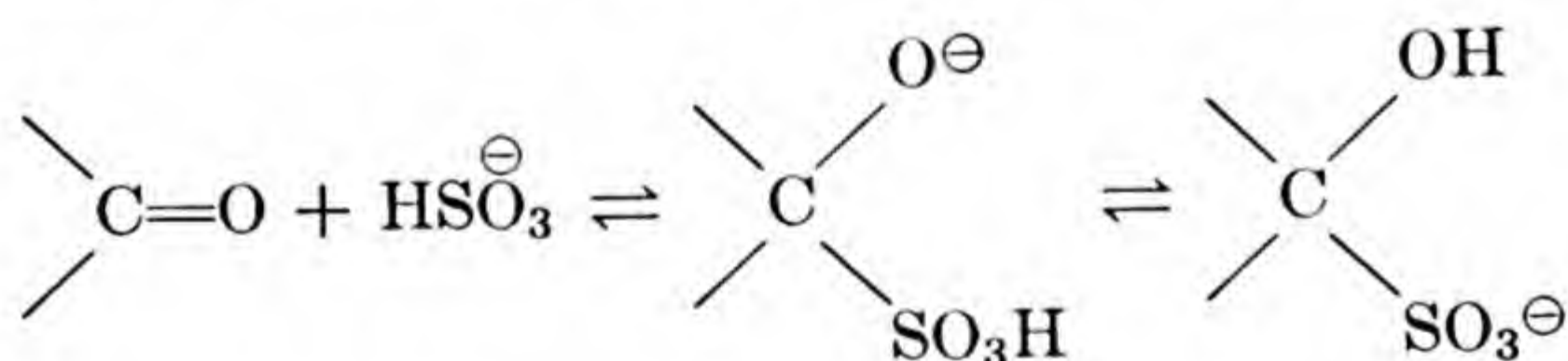
addition of the Grignard reagent  $\text{RMgX}$ . When it is realized that aldehydes and ketones are best represented as resonance hybrids in which the contributions of the two structures are approximately equal the course of the reaction becomes evident.



The addition of hydrogen cyanide probably occurs as shown in the following equations:

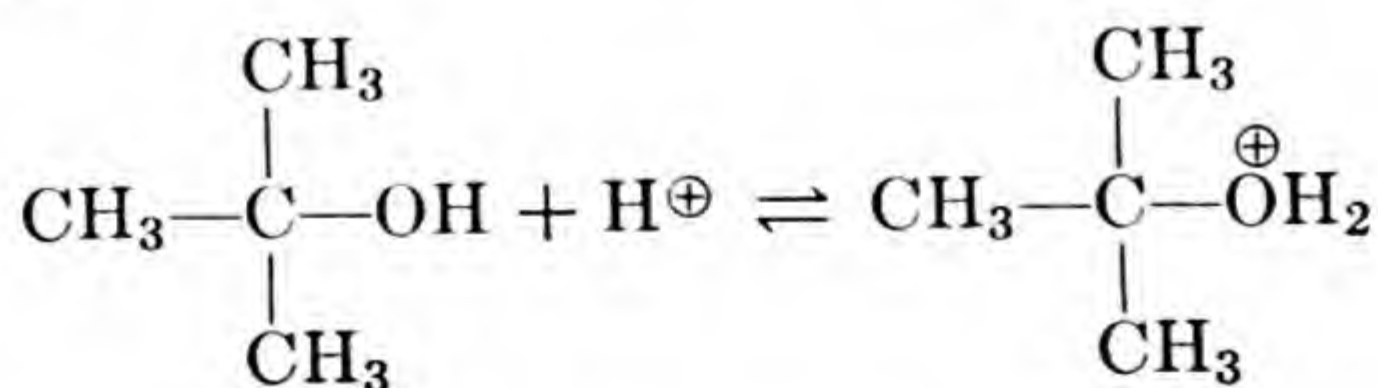


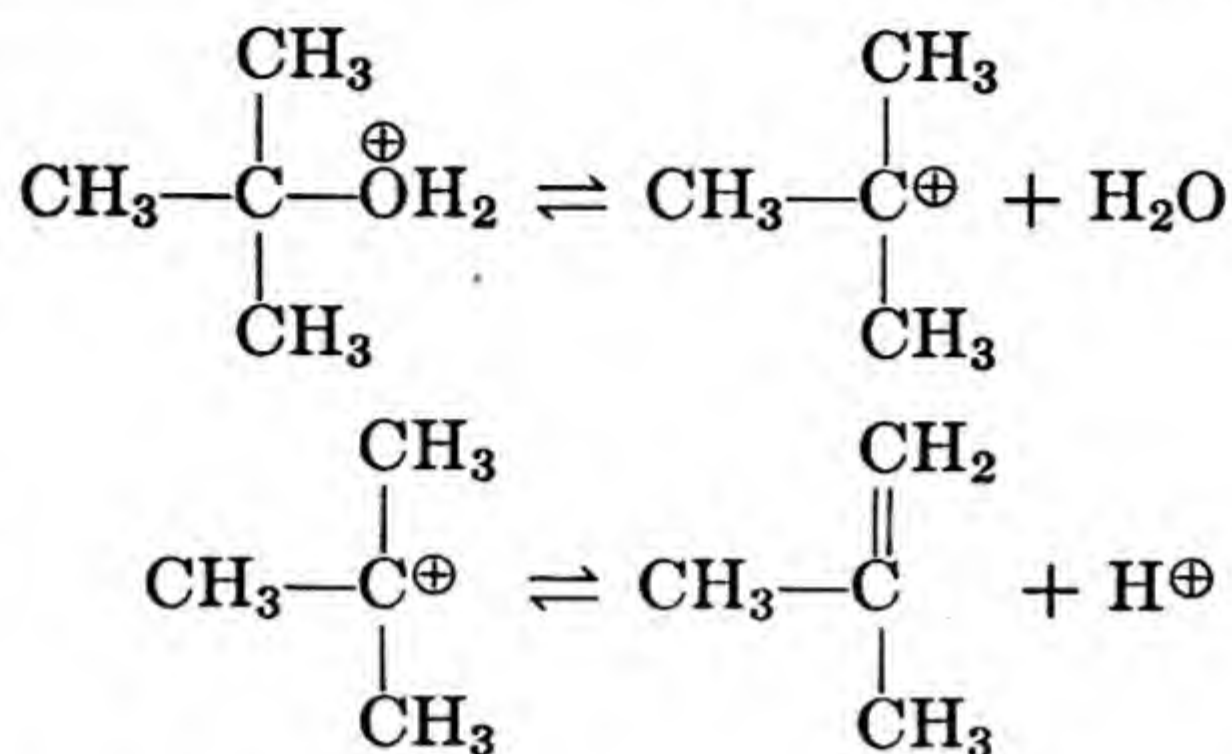
The formation of bisulfite addition products can be written as



The aldol condensation and related reactions proceed by similar but more complex mechanisms.

**Dehydration of Alcohols.** When an alcohol is treated with a strong acid an oxonium ion is formed which can lose a molecule of water to yield a carbonium ion; this in turn can expel a proton to yield an olefin.

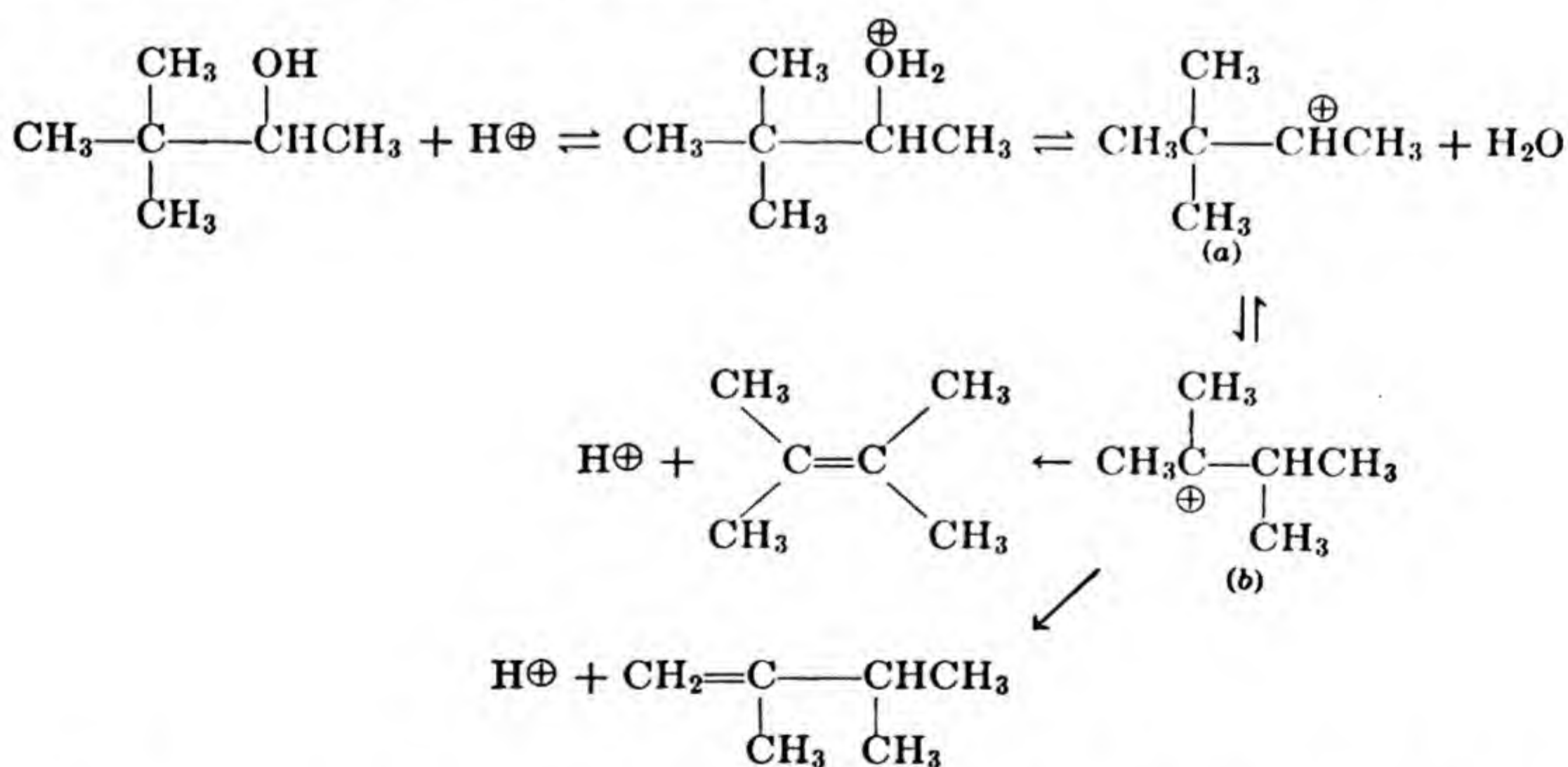




The acid is thus catalytic. The success of the reaction, however, is dependent upon the concentration of the acid, for when much water is present the competition between the water molecules and the alcohol molecules for the protons from the acid is unfavorable to the production of alcohol oxonium ions.

The loss of a proton from a carbonium ion to yield an olefin is not the only way this ion may be stabilized. It may, for example, react with an anion or with the solvent, undergo rearrangement, or acquire a hydride ion ( $\text{H}:\ominus$ ) from some substance present. Carbonium ions are intermediates in many reactions, and a knowledge of their behavior is valuable, since many apparently different reactions have mechanistic similarities.

The Wagner-Meerwein rearrangement is an alcohol dehydration in which rearrangement of the carbon skeleton occurs. It is illustrated here with pinacolyl alcohol:

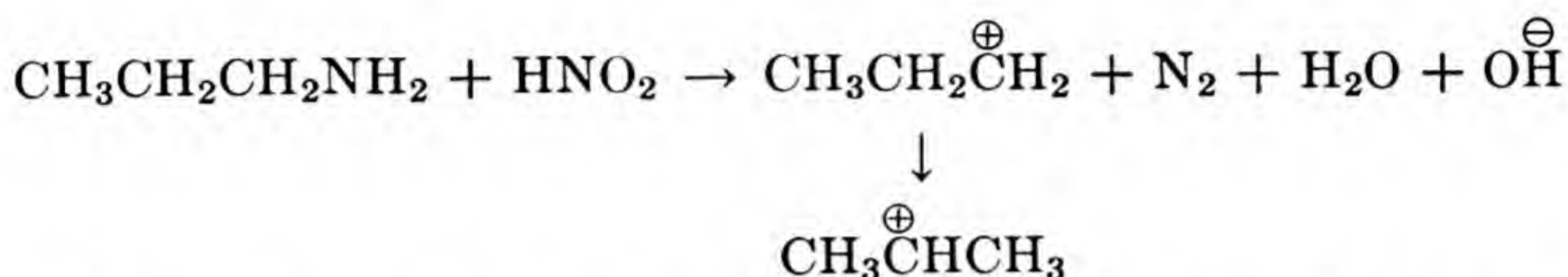


The rearrangement occurs in the conversion of carbonium ion *a* to *b*, which involves the transfer of a methyl group with a pair of electrons. The new carbonium ion *b* is tertiary, and as a rule the

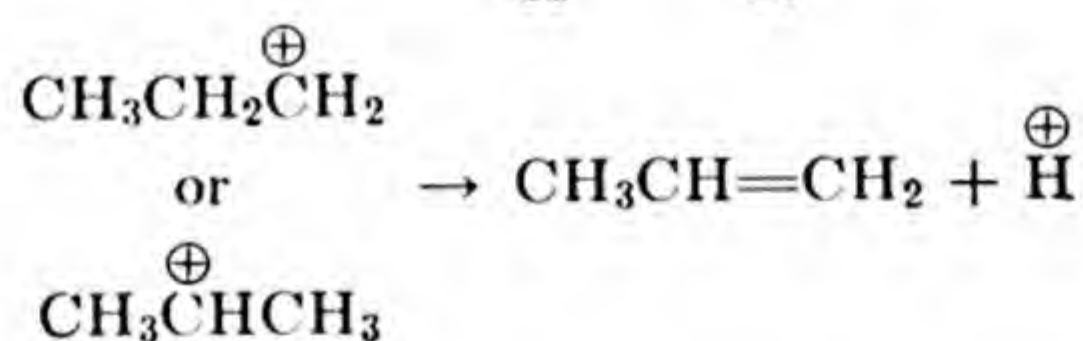
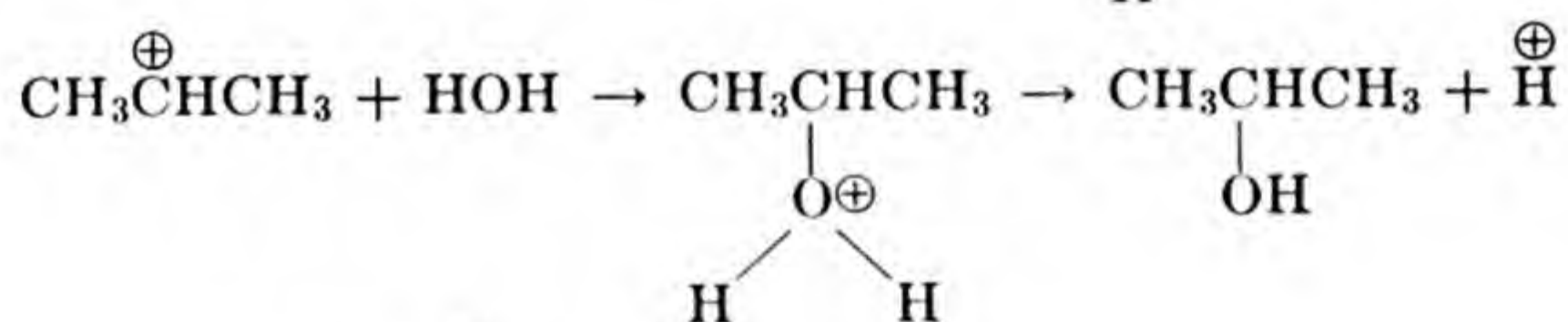
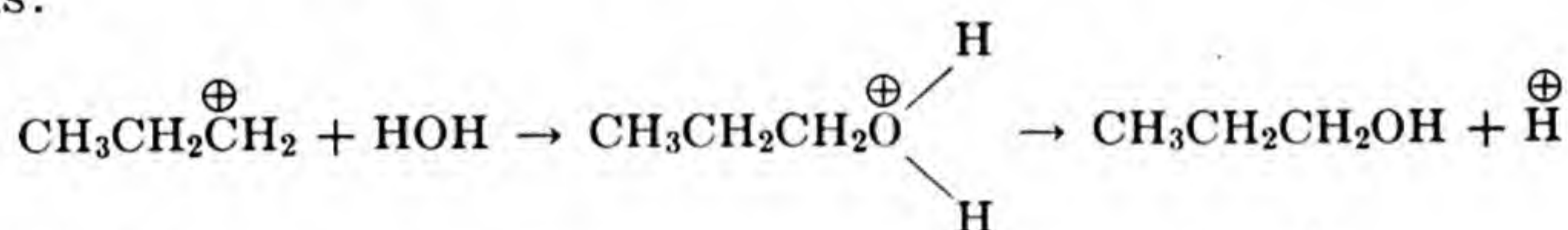


stability of carbonium ions is greatest in the tertiary and least in the primary type. The final stabilization occurs by loss of a proton. This can and does take place in two different ways to give the two olefins, though the predominant product is 2,3-dimethyl-2-butene.

The reaction of nitrous acid with primary aliphatic amines provides another example in which a carbonium ion is an intermediate.



Stabilization occurs in several ways, and the products, in order of decreasing quantities, are isopropyl alcohol, *n*-propyl alcohol, and propylene. They are probably produced according to the following equations:



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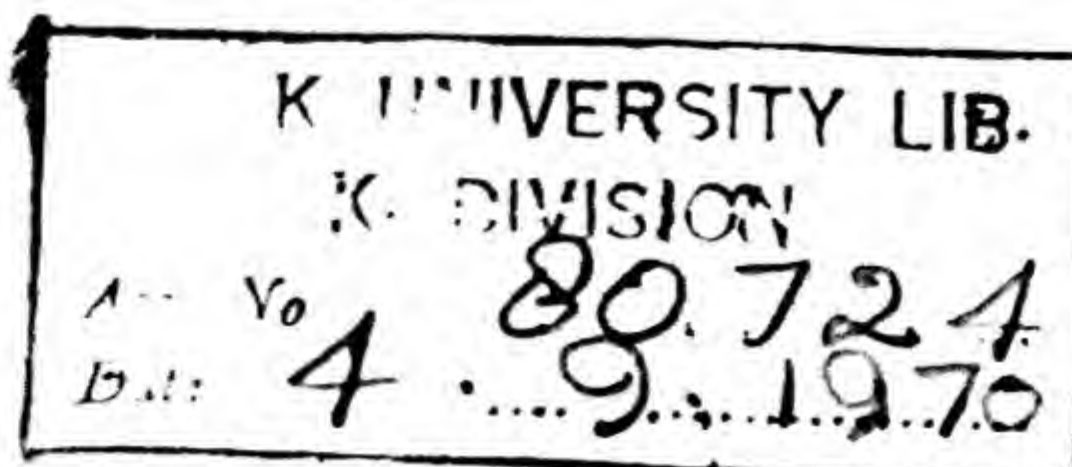
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